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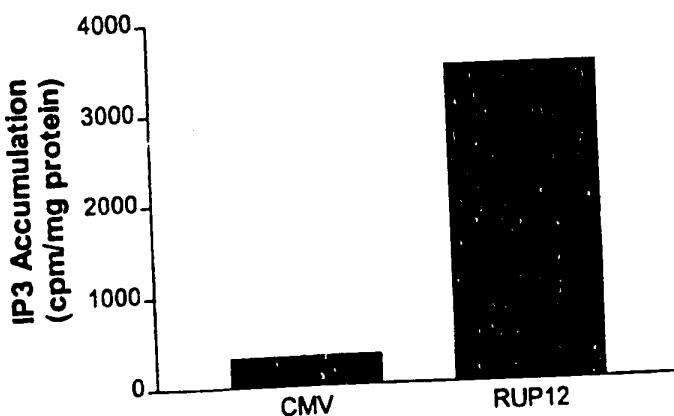
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(54) Title: ENDOGENOUS AND NON-ENDOGENOUS VERSIONS OF HUMAN G PROTEIN-COUPLED RECEPTORS

IP3 Assay in 293 Cells

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(57) Abstract: The invention disclosed in this patent document relates to transmembrane receptors, more particularly to a human G protein-coupled receptor for which the endogenous ligand is unknown ("orphan GPCR receptors"), and most particularly to mutated (non-endogenous) versions of the human GPCRs for evidence of constitutive activity.



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ENDOGENOUS AND NON-ENDOGENOUS VERSIONS OF HUMAN G PROTEIN-COUPLED RECEPTORS

FIELD OF THE INVENTION

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The invention disclosed in this patent document relates to transmembrane receptors, and more particularly to human G protein-coupled receptors, and specifically to endogenous human GPCRs with particular emphasis on non-endogenous versions of the GPCRs that have been altered to establish or enhance 10 constitutive activity of the receptor. Preferably, the altered GPCRs are used for the direct identification of candidate compounds as receptor agonists, inverse agonists or partial agonists having potential applicability as therapeutic agents.

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BACKGROUND OF THE INVENTION

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Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR or GPCRs) class. It is estimated that there are some 100,000 genes within the human genome, and of these, approximately 2%, or 2,000 genes, are estimated to code for GPCRs. Receptors, including GPCRs, for which the endogenous ligand has been identified are referred to as "known" receptors, while receptors for which the endogenous ligand has not been identified are referred to as "orphan" receptors. GPCRs represent an important area for the development of pharmaceutical products: from 25 approximately 20 of the 100 known GPCRs, approximately 60% of all prescription pharmaceuticals have been developed.

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GPCRs share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane (each span is identified by number, *i.e.*, transmembrane-1 (TM-1), transmembrane-2 (TM-2), etc.). The transmembrane helices are joined by strands of amino acids between transmembrane-2 and transmembrane-3,

transmembrane-4 and transmembrane-5, and transmembrane-6 and transmembrane-7 on the exterior, or "extracellular" side, of the cell membrane (these are referred to as "extracellular" regions 1, 2 and 3 (EC-1, EC-2 and EC-3), respectively). The transmembrane helices are also joined by strands of amino acids between transmembrane-1 and transmembrane-2, transmembrane-3 and transmembrane-4, and transmembrane-5 and transmembrane-6 on the interior, or "intracellular" side, of the cell membrane (these are referred to as "intracellular" regions 1, 2 and 3 (IC-1, IC-2 and IC-3), respectively). The "carboxy" ("C") terminus of the receptor lies in the intracellular space within the cell, and the "amino" ("N") terminus of the receptor lies in the extracellular space outside of the cell.

Generally, when an endogenous ligand binds with the receptor (often referred to as "activation" of the receptor), there is a change in the conformation of the intracellular region that allows for coupling between the intracellular region and an intracellular "G-protein." It has been reported that GPCRs are "promiscuous" with respect to G proteins, i.e., that a GPCR can interact with more than one G protein. See, Kenakin, T., 43 *Life Sciences* 1095 (1988). Although other G proteins exist, currently, Gq, Gs, Gi, Gz and Go are G proteins that have been identified. Endogenous ligand-activated GPCR coupling with the G-protein begins a signaling cascade process (referred to as "signal transduction"). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition. It is thought that the IC-3 loop as well as the carboxy terminus of the receptor interact with the G protein.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular signaling transduction pathway to produce a biological response. Changing the receptor

conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response.

A receptor may be stabilized in an active state by an endogenous ligand or a compound such as a drug. Recent discoveries, including but not exclusively limited to 5 modifications to the amino acid sequence of the receptor, provide means other than endogenous ligands or drugs to promote and stabilize the receptor in the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of an endogenous ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

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SUMMARY OF THE INVENTION

Disclosed herein are endogenous and non-endogenous versions of human GPCRs and uses thereof.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides an illustration of second messenger IP₃ production from endogenous version RUP12 ("RUP12") as compared with the control ("CMV").

Figure 2 is a graphic representation of the results of a second messenger cell-based cyclic AMP assay providing comparative results for constitutive signaling of 20 endogenous RUP13 ("RUP13") and a control vector ("CMV").

Figure 3 is a diagrammatic representation of the signal measured comparing CMV, endogenous RUP13 ("RUP13 wt") and non-endogenous, constitutively activated RUP13 ("RUP13(A268K)"), utilizing 8XCRE-Luc reporter plasmid.

Figure 4 is a graphic representation of the results of a [³⁵S]GTPγS assay providing comparative results for constitutive signaling by RUP13:Gs Fusion Protein ("RUP13-Gs") and a control vector ("CMV").

5 **Figure 5** is a diagrammatic representation of the signal measured comparing CMV, endogenous RUP14 ("RUP14 wt") and non-endogenous, constitutively activated RUP13 ("RUP14(L246K)"), utilizing 8XCRE-Luc reporter plasmid.

Figure 6 is a diagrammatic representation of the signal measured comparing CMV, endogenous RUP15 ("RUP15 wt") and non-endogenous, constitutively activated RUP15 ("RUP15(A398K)"), utilizing 8XCRE-Luc reporter plasmid.

10 **Figure 7** is a graphic representation of the results of a second messenger cell-based cyclic AMP assay providing comparative results for constitutive signaling of endogenous RUP15 ("RUP15 wt"), non-endogenous, constitutively activated version of RUP15 ("RUP15(A398K)") and a control vector ("CMV").

15 **Figure 8** is a graphic representation of the results of a [³⁵S]GTPγS assay providing comparative results for constitutive signaling by RUP15:Gs Fusion Protein ("RUP15-Gs") and a control vector ("CMV").

Figure 9 provides an illustration of second messenger IP₃ production from endogenous version RUP17 ("RUP17") as compared with the control ("CMV").

20 **Figure 10** provides an illustration of second messenger IP₃ production from endogenous version RUP21 ("RUP21") as compared with the control ("CMV").

Figure 11 is a diagrammatic representation of the signal measured comparing CMV, endogenous RUP23 ("RUP23 wt") and non-endogenous, constitutively activated RUP23 ("RUP23(W275K)"), utilizing 8XCRE-Luc reporter plasmid.

Figure 12 is a graphic representation of results from a primary screen of several candidate compounds against RUP13; results for "Compound A" are provided in well A2 and "Compound "B" are provided in well G9.

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DETAILED DESCRIPTION

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the 10 following definitions shall control:

AGONISTS shall mean materials (e.g., ligands, candidate compounds) that activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes.

AMINO ACID ABBREVIATIONS used herein are set out in Table A:

TABLE A

ALANINE	ALA	A
ARGININE	ARG	R
ASPARAGINE	ASN	N
ASPARTIC ACID	ASP	D
CYSTEINE	CYS	C
GLUTAMIC ACID	GLU	E
GLUTAMINE	GLN	Q
GLYCINE	GLY	G
HISTIDINE	HIS	H
ISOLEUCINE	ILE	I
LEUCINE	LEU	L
LYSINE	LYS	K
METHIONINE	MET	M

PHENYLALANINE	PHE	F
PROLINE	PRO	P
SERINE	SER	S
THREONINE	THR	T
TRYPTOPHAN	TRP	W
TYROSINE	TYR	Y
VALINE	VAL	V

PARTIAL AGONISTS shall mean materials (e.g., ligands, candidate compounds) that activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser

5 degree/extent than do agonists.

ANTAGONIST shall mean materials (e.g., ligands, candidate compounds) that competitively bind to the receptor at the same site as the agonists but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists.

10 **ANTAGONISTS** do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

CANDIDATE COMPOUND shall mean a molecule (for example, and not limitation, a chemical compound) that is amenable to a screening technique. Preferably, the phrase "candidate compound" does not include compounds which were publicly known to be compounds selected from the group consisting of inverse agonist, agonist or antagonist to a receptor, as previously determined by an indirect identification process ("indirectly identified compound"); more preferably, not including an indirectly identified compound which has previously been determined to have therapeutic efficacy in at least one mammal; and, most preferably, not including an indirectly identified compound which has previously been determined to have therapeutic utility in humans.

COMPOSITION means a material comprising at least one component; a "pharmaceutical composition" is an example of a composition.

COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity. Exemplary means of detecting compound efficacy are disclosed in the Example 5 section of this patent document.

CODON shall mean a grouping of three nucleotides (or equivalents to 10 nucleotides) which generally comprise a nucleoside (adenosine (A), guanosine (G), cytidine (C), uridine (U) and thymidine (T)) coupled to a phosphate group and which, when translated, encodes an amino acid.

CONSTITUTIVELY ACTIVATED RECEPTOR shall mean a receptor subject to constitutive receptor activation. A constitutively activated receptor can be endogenous or non-endogenous.

CONSTITUTIVE RECEPTOR ACTIVATION shall mean stabilization of a 15 receptor in the active state by means other than binding of the receptor with its endogenous ligand or a chemical equivalent thereof.

CONTACT or **CONTACTING** shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system.

DIRECTLY IDENTIFYING or **DIRECTLY IDENTIFIED**, in relationship to 20 the phrase "candidate compound", shall mean the screening of a candidate compound against a constitutively activated receptor, preferably a constitutively activated orphan receptor, and most preferably against a constitutively activated G protein-coupled cell surface orphan receptor, and assessing the compound efficacy of such compound. This phrase is, under no circumstances, to be interpreted or understood to be encompassed by 25 or to encompass the phrase "indirectly identifying" or "indirectly identified."

ENDOGENOUS shall mean a material that a mammal naturally produces. **ENDOGENOUS** in reference to, for example and not limitation, the term "receptor," shall mean that which is naturally produced by a mammal (for example, and not limitation, a human) or a virus. By contrast, the term **NON-ENDOGENOUS** in this context shall mean that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus. For example, and not limitation, a receptor which is not constitutively active in its endogenous form, but when manipulated becomes constitutively active, is most preferably referred to herein as a "non-endogenous, constitutively activated receptor." Both terms can be utilized to describe both "in vivo" and "in vitro" systems. For example, and not limitation, in a screening approach, the endogenous or non-endogenous receptor may be in reference to an in vitro screening system. As a further example and not limitation, where the genome of a mammal has been manipulated to include a non-endogenous constitutively activated receptor, screening of a candidate compound by means of an in vivo system is viable.

15 G PROTEIN COUPLED RECEPTOR FUSION PROTEIN and GPCR FUSION PROTEIN, in the context of the invention disclosed herein, each mean a non-endogenous protein comprising an endogenous, constitutively activate GPCR or a non-endogenous, constitutively activated GPCR fused to at least one G protein, most preferably the alpha (α) subunit of such G protein (this being the subunit that binds GTP), with the G protein preferably being of the same type as the G protein that naturally couples with endogenous orphan GPCR. For example, and not limitation, in an endogenous state, if the G protein "G α " is the predominate G protein that couples with the GPCR, a GPCR Fusion Protein based upon the specific GPCR would be a non-endogenous protein comprising the GPCR fused to G α ; in some circumstances, as will be set forth below, a non-predominant G protein can be fused to the GPCR. The G

protein can be fused directly to the c-terminus of the constitutively active GPCR or there may be spacers between the two.

HOST CELL shall mean a cell capable of having a Plasmid and/or Vector incorporated therein. In the case of a prokaryotic Host Cell, a Plasmid is typically 5 replicated as a autonomous molecule as the Host Cell replicates (generally, the Plasmid is thereafter isolated for introduction into a eukaryotic Host Cell); in the case of a eukaryotic Host Cell, a Plasmid is integrated into the cellular DNA of the Host Cell such that when the eukaryotic Host Cell replicates, the Plasmid replicates. Preferably, for the purposes of the invention disclosed herein, the Host Cell is eukaryotic, more preferably, 10 mammalian, and most preferably selected from the group consisting of 293, 293T and COS-7 cells.

INDIRECTLY IDENTIFYING or **INDIRECTLY IDENTIFIED** means the traditional approach to the drug discovery process involving identification of an endogenous ligand specific for an endogenous receptor, screening of candidate 15 compounds against the receptor for determination of those which interfere and/or compete with the ligand-receptor interaction, and assessing the efficacy of the compound for affecting at least one second messenger pathway associated with the activated receptor.

INHIBIT or **INHIBITING**, in relationship to the term "response" shall mean 20 that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

INVERSE AGONISTS shall mean materials (e.g., ligand, candidate compound) which bind to either the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response 25 initiated by the active form of the receptor below the normal base level of activity which

is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse 5 agonist.

KNOWN RECEPTOR shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has been identified.

LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

10 **MUTANT** or **MUTATION** in reference to an endogenous receptor's nucleic acid and/or amino acid sequence shall mean a specified change or changes to such endogenous sequences such that a mutated form of an endogenous, non-constitutively activated receptor evidences constitutive activation of the receptor. In terms of equivalents to specific sequences, a subsequent mutated form of a human receptor is 15 considered to be equivalent to a first mutation of the human receptor if (a) the level of constitutive activation of the subsequent mutated form of a human receptor is substantially the same as that evidenced by the first mutation of the receptor; and (b) the percent sequence (amino acid and/or nucleic acid) homology between the subsequent mutated form of the receptor and the first mutation of the receptor is at least about 80%, 20 more preferably at least about 90% and most preferably at least 95%. Ideally, and owing to the fact that the most preferred cassettes disclosed herein for achieving constitutive activation includes a single amino acid and/or codon change between the endogenous and the non-endogenous forms of the GPCR, the percent sequence homology should be at least 98%.

NON-ORPHAN RECEPTOR shall mean an endogenous naturally occurring molecule specific for an endogenous naturally occurring ligand wherein the binding of a ligand to a receptor activates an intracellular signaling pathway.

ORPHAN RECEPTOR shall mean an endogenous receptor for which the 5 endogenous ligand specific for that receptor has not been identified or is not known.

PHARMACEUTICAL COMPOSITION shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the 10 techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

PLASMID shall mean the combination of a Vector and cDNA. Generally, a Plasmid is introduced into a Host Cell for the purposes of replication and/or expression of the cDNA as a protein.

15 **SECOND MESSENGER** shall mean an intracellular response produced as a result of receptor activation. A second messenger can include, for example, inositol triphosphate (IP₃), diacylglycerol (DAG), cyclic AMP (cAMP), and cyclic GMP (cGMP). Second messenger response can be measured for a determination of receptor activation. In addition, second messenger response can be measured for the direct 20 identification of candidate compounds, including for example, inverse agonists, agonists, partial agonists and antagonists.

STIMULATE or **STIMULATING**, in relationship to the term "response" shall mean that a response is increased in the presence of a compound as opposed to in the absence of the compound.

VECTOR in reference to cDNA shall mean a circular DNA capable of incorporating at least one cDNA and capable of incorporation into a Host Cell.

The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to

5 follow.

A. Introduction

The traditional study of receptors has always proceeded from the a priori assumption (historically based) that the endogenous ligand must first be identified before

10 discovery could proceed to find antagonists and other molecules that could affect the receptor. Even in cases where an antagonist might have been known first, the search immediately extended to looking for the endogenous ligand. This mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors. What has not been heretofore recognized is that it is the active state of the

15 receptor that is most useful for discovering agonists, partial agonists, and inverse agonists of the receptor. For those diseases which result from an overly active receptor or an under-active receptor, what is desired in a therapeutic drug is a compound which acts to diminish the active state of a receptor or enhance the activity of the receptor, respectively, not necessarily a drug which is an antagonist to the endogenous ligand.

20 This is because a compound that reduces or enhances the activity of the active receptor state need not bind at the same site as the endogenous ligand. Thus, as taught by a method of this invention, any search for therapeutic compounds should start by screening compounds against the ligand-independent active state.

25 B. Identification of Human GPCRs

The efforts of the Human Genome project has led to the identification of a plethora of information regarding nucleic acid sequences located within the human genome; it has been the case in this endeavor that genetic sequence information has been made available without an understanding or recognition as to whether or not any particular genomic sequence does or may contain open-reading frame information that translate human proteins. Several methods of identifying nucleic acid sequences within the human genome are within the purview of those having ordinary skill in the art. For example, and not limitation, a variety of human GPCRs, disclosed herein, were discovered by reviewing the GenBank™ database. Table B, below, lists several 10 endogenous GPCRs that we have discovered, along with other GPCR's that are homologous to the disclosed GPCR.

TABLE B

Disclosed Human Orphan GPCRs	Accession Number Identified	Open Reading Frame (Base Pairs)	Reference To Homologous GPCR	Per Cent Homology To Designated GPCR
hRUP8	AL121755	1,152bp	NPY2R	27%
hRUP9	AC0113375	1,260bp	GAL2R	22%
hRUP10	AC008745	1,014bp	C5aR	40%
hRUP11	AC013396	1,272bp	HM74	36%
hRUP12	AP000808	966bp	Mas1	34%
hRUP13	AC011780	1,356bp	Fish GPRX-ORYLA	43%
hRUP14	AL137118	1,041bp	CysLT1R	35%
hRUP15	AL016468	1,527bp	RE2	30%
hRUP16	AL136106	1,068bp	GLR101	37%
hRUP17	AC023078	969bp	Mas1	37%
hRUP18	AC008547	1,305bp	Oxytocin	31%
hRUP19	AC026331	1,041bp	HM74	52%
hRUP20	AL161458	1,011bp	GPR34	25%
hRUP21	AC026756	1,014bp	P2Y1R	37%
hRUP22	AC027026	993bp	RUP17 Mas1	67% 37%

hRUP23	AC007104	1,092bp	Rat GPR26	31%
hRUP24	AL355388	1,125bp	SALPR	44%
hRUP25	AC026331	1,092bp	HM74	95%
hRUP26	AC023040	1,044bp	Rabbit 5HT1D	27%
hRUP27	AC027643	158,700	MCH	38%

Receptor homology is useful in terms of gaining an appreciation of a role of the receptors within the human body. As the patent document progresses, we will disclose techniques for mutating these receptors to establish non-endogenous, constitutively activated versions of these receptors.

The techniques disclosed herein have also been applied to other human, orphan GPCRs known to the art, as will be apparent as the patent document progresses.

C. Receptor Screening

Screening candidate compounds against a non-endogenous, constitutively activated version of the human GPCRs disclosed herein allows for the direct identification of candidate compounds which act at this cell surface receptor, without requiring use of the receptor's endogenous ligand. Using routine, and often commercially available techniques, one can determine areas within the body where the endogenous version of human GPCRs disclosed herein is expressed and/or over-expressed. It is also possible using these techniques to determine related disease/disorder states which are associated with the expression and/or over-expression of the receptor; such an approach is disclosed in this patent document.

With respect to creation of a mutation that may evidence constitutive activation of the human GPCR disclosed herein is based upon the distance from the proline residue at which is presumed to be located within TM6 of the GPCR; this algorithmic technique is disclosed in co-pending and commonly assigned patent document PCT Application

Number PCT/US99/23938, published as WO 00/22129 on April 20, 2000, which, along with the other patent documents listed herein, is incorporated herein by reference. The algorithmic technique is not predicated upon traditional sequence "alignment" but rather a specified distance from the aforementioned TM6 proline residue (or, of course, 5 endogenous constitutive substitution for such proline residue). By mutating the amino acid residue located 16 amino acid residues from this residue (presumably located in the IC3 region of the receptor) to, most preferably, a lysine residue, such activation may be obtained. Other amino acid residues may be useful in the mutation at this position to achieve this objective.

10

D. Disease/Disorder Identification and/or Selection

As will be set forth in greater detail below, most preferably inverse agonists and agonists to the non-endogenous, constitutively activated GPCR can be identified by the methodologies of this invention. Such inverse agonists and agonists are ideal candidates 15 as lead compounds in drug discovery programs for treating diseases related to this receptor. Because of the ability to directly identify inverse agonists to the GPCR, thereby allowing for the development of pharmaceutical compositions, a search for diseases and disorders associated with the GPCR is relevant. For example, scanning both diseased and normal tissue samples for the presence of the GPCR now becomes 20 more than an academic exercise or one which might be pursued along the path of identifying an endogenous ligand to the specific GPCR. Tissue scans can be conducted across a broad range of healthy and diseased tissues. Such tissue scans provide a preferred first step in associating a specific receptor with a disease and/or disorder.

Preferably, the DNA sequence of the human GPCR is used to make a probe for 25 (a) dot-blot analysis against tissue-mRNA, and/or (b) RT-PCR identification of the expression of the receptor in tissue samples. The presence of a receptor in a tissue

source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be preferably utilized to identify a correlation with a treatment regimen, including but not limited to, a disease associated with that disease. Receptors can equally well be localized to regions of organs by this 5 technique. Based on the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced.

E. Screening of Candidate Compounds

1. Generic GPCR screening assay techniques

10 When a G protein receptor becomes constitutively active, it binds to a G protein (e.g., Gq, Gs, Gi, Gz, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes deactivated. However, constitutively activated receptors continue to exchange GDP to GTP. A non-hydrolyzable analog of 15 GTP, [³⁵S]GTPγS, can be used to monitor enhanced binding to membranes which express constitutively activated receptors. It is reported that [³⁵S]GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among other examples well-known and available to those in the art, was reported by Traynor and Nahorski in 1995. The preferred use of this assay 20 system is for initial screening of candidate compounds because the system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor.

2. Specific GPCR screening assay techniques

Once candidate compounds are identified using the "generic" G protein-coupled 25 receptor assay (*i.e.*, an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the

receptor site is preferred. For example, a compound identified by the "generic" assay may not bind to the receptor, but may instead merely "uncouple" the G protein from the intracellular domain.

a. Gs, Gz and Gi.

5 Gs stimulates the enzyme adenylyl cyclase. Gi (and Gz and Go), on the other hand, inhibit this enzyme. Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, constitutively activated GPCRs that couple the Gs protein are associated with increased cellular levels of cAMP. On the other hand, constitutively activated GPCRs that couple Gi (or Gz, Go) protein are associated with decreased cellular levels of cAMP.

10 See, generally, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Thus, assays that detect cAMP can be utilized to determine if a candidate compound is, e.g., an inverse agonist to the receptor (*i.e.*, such a compound would decrease the levels of cAMP). A variety of approaches known in the art for measuring cAMP can be utilized;

15 a most preferred approach relies upon the use of anti-cAMP antibodies in an ELISA-based format. Another type of assay that can be utilized is a whole cell second messenger reporter system assay. Promoters on genes drive the expression of the proteins that a particular gene encodes. Cyclic AMP drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or transcription

20 factor (CREB) that then binds to the promoter at specific sites called cAMP response elements and drives the expression of the gene. Reporter systems can be constructed which have a promoter containing multiple cAMP response elements before the reporter gene, *e.g.*, β -galactosidase or luciferase. Thus, a constitutively activated Gs-linked receptor causes the accumulation of cAMP that then activates the gene and expression of

the reporter protein. The reporter protein such as β -galactosidase or luciferase can then be detected using standard biochemical assays (Chen et al. 1995).

b. Go and Gq.

5 Gq and Go are associated with activation of the enzyme phospholipase C, which in turn hydrolyzes the phospholipid PIP₂, releasing two intracellular messengers: diacycloglycerol (DAG) and inistol 1,4,5-triphosphate (IP₃). Increased accumulation of IP₃ is associated with activation of Gq- and Go-associated receptors. *See, generally, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992).* Assays that detect IP₃ 10 accumulation can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to a Gq- or Go-associated receptor (*i.e.*, such a compound would decrease the levels of IP₃). Gq-associated receptors can also been examined using an AP1 reporter assay in that Gq-dependent phospholipase C causes activation of genes containing AP1 15 elements; thus, activated Gq-associated receptors will evidence an increase in the expression of such genes, whereby inverse agonists thereto will evidence a decrease in such expression, and agonists will evidence an increase in such expression. Commercially available assays for such detection are available.

3. GPCR Fusion Protein

20 The use of an endogenous, constitutively activate orphan GPCR or a non-endogenous, constitutively activated orphan GPCR, for use in screening of candidate compounds for the direct identification of inverse agonists, agonists and partial agonists provide an interesting screening challenge in that, by definition, the receptor is active even in the absence of an endogenous ligand bound thereto. Thus, in order to 25 differentiate between, *e.g.*, the non-endogenous receptor in the presence of a candidate compound and the non-endogenous receptor in the absence of that compound, with an

aim of such a differentiation to allow for an understanding as to whether such compound may be an inverse agonist, agonist, partial agonist or have no affect on such a receptor, it is preferred that an approach be utilized that can enhance such differentiation. A preferred approach is the use of a GPCR Fusion Protein.

5 Generally, once it is determined that a non-endogenous orphan GPCR has been constitutively activated using the assay techniques set forth above (as well as others), it is possible to determine the predominant G protein that couples with the endogenous GPCR. Coupling of the G protein to the GPCR provides a signaling pathway that can be assessed. Because it is most preferred that screening take place by use of a mammalian 10 expression system, such a system will be expected to have endogenous G protein therein. Thus, by definition, in such a system, the non-endogenous, constitutively activated orphan GPCR will continuously signal. In this regard, it is preferred that this signal be enhanced such that in the presence of, *e.g.*, an inverse agonist to the receptor, it is more likely that it will be able to more readily differentiate, particularly in the context of 15 screening, between the receptor when it is contacted with the inverse agonist.

The GPCR Fusion Protein is intended to enhance the efficacy of G protein coupling with the non-endogenous GPCR. The GPCR Fusion Protein is preferred for screening with a non-endogenous, constitutively activated GPCR because such an approach increases the signal that is most preferably utilized in such screening 20 techniques. This is important in facilitating a significant "signal to noise" ratio; such a significant ratio is import preferred for the screening of candidate compounds as disclosed herein.

The construction of a construct useful for expression of a GPCR Fusion Protein is within the purview of those having ordinary skill in the art. Commercially available 25 expression vectors and systems offer a variety of approaches that can fit the particular

needs of an investigator. The criteria of importance for such a GPCR Fusion Protein construct is that the endogenous GPCR sequence and the G protein sequence both be in-frame (preferably, the sequence for the endogenous GPCR is upstream of the G protein sequence) and that the "stop" codon of the GPCR must be deleted or replaced such that 5 upon expression of the GPCR, the G protein can also be expressed. The GPCR can be linked directly to the G protein, or there can be spacer residues between the two (preferably, no more than about 12, although this number can be readily ascertained by one of ordinary skill in the art). We have a preference (based upon convenience) of use of a spacer in that some restriction sites that are not used will, effectively, upon 10 expression, become a spacer. Most preferably, the G protein that couples to the non-endogenous GPCR will have been identified prior to the creation of the GPCR Fusion Protein construct. Because there are only a few G proteins that have been identified, it is preferred that a construct comprising the sequence of the G protein (*i.e.*, a universal G protein construct) be available for insertion of an endogenous GPCR sequence therein; 15 this provides for efficiency in the context of large-scale screening of a variety of different endogenous GPCRs having different sequences.

As noted above, constitutively activated GPCRs that couple to Gi, Gz and Go are expected to inhibit the formation of cAMP making assays based upon these types of GPCRs challenging (*i.e.*, the cAMP signal decreases upon activation thus making the 20 direct identification of, *e.g.*, inverse agonists (which would further decrease this signal), interesting. As will be disclosed herein, we have ascertained that for these types of receptors, it is possible to create a GPCR Fusion Protein that is not based upon the endogenous GPCR's endogenous G protein, in an effort to establish a viable cyclase-based assay. Thus, for example, an endogenous Gi coupled receptor can be fused to a Gs 25 protein – we believe that such a fusion construct, upon expression, "drives" or "forces"

the endogenous GPCR to couple with, *e.g.*, Gs rather than the "natural" Gi protein, such that a cyclase-based assay can be established. Thus, for Gi, Gz and Go coupled receptors, we prefer that when a GPCR Fusion Protein is used and the assay is based upon detection of adenylyl cyclase activity, that the fusion construct be established with 5 Gs (or an equivalent G protein that stimulates the formation of the enzyme adenylyl cyclase).

Equally effective is a G Protein Fusion construct that utilizes a Gq Protein fused with a Gs, Gi, Gz or Go Protein. A most preferred fusion construct can be accomplished with a Gq Protein wherein the first six (6) amino acids of the G-protein α -subunit 10 ("G α q") is deleted and the last five (5) amino acids at the C-terminal end of G α q is replaced with the corresponding amino acids of the G α of the G protein of interest. For example, a fusion construct can have a Gq (6 amino acid deletion) fused with a Gi Protein, resulting in a "Gq/Gi Fusion Construct". We believe that this fusion construct 15 will force the endogenous Gi coupled receptor to couple to its non-endogenous G protein, Gq, such that the second messenger, for example, inositol triphosphate or diacylglycerol, can be measured in lieu of cAMP production.

4. Co-transfection of a Target Gi Coupled GPCR with a Signal-Enhancer Gs Coupled GPCR (cAMP Based Assays)

20 A Gi coupled receptor is known to inhibit adenylyl cyclase, and, therefore, decrease the level of cAMP production, which can make assessment of cAMP levels challenging. An effective technique in measuring the decrease in production of cAMP as an indication of constitutive activation of a receptor that predominantly couples Gi upon 25 activation can be accomplished by co-transfected a signal enhancer, *e.g.*, a non-endogenous, constitutively activated receptor that predominantly couples with Gs upon activation (*e.g.*, TSHR-A623I, disclosed below), with the Gi linked GPCR. As is

apparent, constitutive activation of a Gs coupled receptor can be determined based upon an increase in production of cAMP. Constitutive activation of a Gi coupled receptor leads to a decrease in production cAMP. Thus, the co-transfection approach is intended to advantageously exploit these "opposite" affects. For example, co-transfection of a 5 non-endogenous, constitutively activated Gs coupled receptor (the "signal enhancer") with the endogenous Gi coupled receptor (the "target receptor") provides a baseline cAMP signal (*i.e.*, although the Gi coupled receptor will decrease cAMP levels, this "decrease" will be relative to the substantial increase in cAMP levels established by constitutively activated Gs coupled signal enhancer). By then co-transfected the signal 10 enhancer with a constitutively activated version of the target receptor, cAMP would be expected to further decrease (relative to base line) due to the increased functional activity of the Gi target (*i.e.*, which decreases cAMP).

Screening of candidate compounds using a cAMP based assay can then be accomplished, with two provisos: first, relative to the Gi coupled target receptor, 15 "opposite" effects will result, *i.e.*, an inverse agonist of the Gi coupled target receptor will increase the measured cAMP signal, while an agonist of the Gi coupled target receptor will decrease this signal; second, as would be apparent, candidate compounds that are directly identified using this approach should be assessed independently to ensure that these do not target the signal enhancing receptor (this can be done prior to or 20 after screening against the co-transfected receptors).

F. Medicinal Chemistry

Generally, but not always, direct identification of candidate compounds is preferably conducted in conjunction with compounds generated via combinatorial 25 chemistry techniques, whereby thousands of compounds are randomly prepared for such analysis. Generally, the results of such screening will be compounds having

unique core structures; thereafter, these compounds are preferably subjected to additional chemical modification around a preferred core structure(s) to further enhance the medicinal properties thereof. Such techniques are known to those in the art and will not be addressed in detail in this patent document.

5

G. Pharmaceutical compositions

Candidate compounds selected for further development can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers are available to those in the art; for example, see 10 Remington's Pharmaceutical Sciences, 16th Edition, 1980, Mack Publishing Co., (Oslo et al., eds.).

H. Other Utility

Although a preferred use of the non-endogenous versions the human GPCRs disclosed herein may be for the direct identification of candidate compounds as inverse 15 agonists, agonists or partial agonists (preferably for use as pharmaceutical agents), these versions of human GPCRs can also be utilized in research settings. For example, *in vitro* and *in vivo* systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, both normal and 20 diseased, as well as understanding the role of constitutive activation as it applies to understanding the signaling cascade. The value in non-endogenous human GPCRs is that their utility as a research tool is enhanced in that, because of their unique features, non-endogenous human GPCRs can be used to understand the role of these receptors in the human body before the endogenous ligand therefore is identified. Other uses of the 25 disclosed receptors will become apparent to those in the art based upon, *inter alia*, a review of this patent document.

EXAMPLES

The following examples are presented for purposes of elucidation, and not limitation, of the present invention. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make minor modifications to these sequences while achieving the same or substantially similar results reported below. The traditional approach to application or understanding of sequence cassettes from one sequence to another (e.g. from rat receptor to human receptor or from human receptor A to human receptor B) is generally predicated upon sequence alignment techniques whereby the sequences are aligned in an effort to determine areas of commonality. The mutational approach disclosed herein does not rely upon this approach but is instead based upon an algorithmic approach and a positional distance from a conserved proline residue located within the TM6 region of human GPCRs. Once this approach is secured, those in the art are credited with the ability to make minor modifications thereto to achieve substantially the same results (*i.e.*, constitutive activation) disclosed herein. Such modified approaches are considered within the purview of this disclosure.

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Example 1
ENDOGENOUS HUMAN GPCRS

1. Identification of Human GPCRs

The disclosed endogenous human GPCRs were identified based upon a review 25 of the GenBank™ database information. While searching the database, the following cDNA clones were identified as evidenced below (Table C).

TABLE C

Disclosed Human Orphan GPCRs	Accession Number Identified	Complete DNA Sequence (Base Pairs)	Open Reading Frame (Base Pairs)	Nucleic Acid SEQ.ID. NO.	Amino Acid SEQ.ID. NO.
hRUP8	AL121755	147,566bp	1,152bp	1	2
hRUP9	AC0113375	143,181bp	1,260bp	3	4
hRUP10	AC008745	94,194bp	1,014bp	5	6
hRUP11	AC013396	155,086bp	1,272bp	7	8
hRUP12	AP000808	177,764bp	966bp	9	10
hRUP13	AC011780	167,819bp	1,356bp	11	12
hRUP14	AL137118	168,297bp	1,041bp	13	14
hRUP15	AL016468	138,828bp	1,527bp	15	16
hRUP16	AL136106	208,042bp	1,068bp	17	18
hRUP17	AC023078	161,735bp	969bp	19	20
hRUP18	AC008547	117,304bp	1,305bp	21	22
hRUP19	AC026331	145,183bp	1,041bp	23	24
hRUP20	AL161458	163,511bp	1,011bp	25	26
hRUP21	AC026756	156,534bp	1,014bp	27	28
hRUP22	AC027026	151,811bp	993bp	29	30
hRUP23	AC007104	200,000bp	1,092bp	31	32
hRUP24	AL355388	190,538bp	1,125bp	33	34
hRUP25	AC026331	145,183bp	1,092bp	35	36
hRUP26	AC023040	178,508bp	1,044bp	37	38
hRUP27	AC027643	158,700bp	1,020bp	39	40

5

2. Full Length Cloning

a. hRUP8 (Seq. Id. Nos. 1 & 2)

The disclosed human RUP8 was identified based upon the use of EST database (*dbEST*) information. While searching the *dbEST*, a cDNA clone with accession number

AL121755 was identified to encode a novel GPCR. The following PCR primers were used for RT-PCR with human testis Marathon-Ready cDNA (Clontech) as templates:

5'-CTTGCAGACATCACCATGGCAGCC-3' (SEQ.ID.NO.:41; sense) and
5'-GTGATGCTCTGAGTACTGGACTGG-3' (SEQ.ID.NO.: 42; antisense).

5 PCR was performed using Advantage cDNA polymerase (Clontech; manufacturing instructions will be followed) in 50ul reaction by the following cycles: 94°C for 30 sec; 94°C for 10 sec; 65°C for 20 sec, 72°C for 1.5 min, and 72°C for 7 min. Cycles 2 through 4 were repeated 35 times.

A 1.2kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem).
10 *See*, SEQ.ID.NO.:1. The putative amino acid sequence for RUP8 is set forth in SEQ.ID.NO.:2.

b. hRUP9 (Seq. Id. Nos. 3 & 4)

The disclosed human RUP9 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC011375 was identified as a human genomic sequence from chromosome 5. The full length RUP9 was cloned by PCR using primers:
15 5'-GAAGCTGTGAAGAGTGATGC-3' (SEQ.ID.NO.:43; sense),
5'-GTCAGCAATATTGATAAGCAGCAG-3' (SEQ.ID.NO.:44; antisense)
20 and human genomic DNA (Promega) as a template. Taq Plus Precision polymerase (Stratagene) was used for the amplification in a 100μl reaction with 5% DMSO by the following cycle with step 2 to step 4 repeated 35 times: 94°C for 1 minute; 94°C for 30 seconds; 56°C for 30 seconds; 72°C for 2 minutes; 72°C for 5 minutes.

A 1.3 Kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) from 1% agarose gel and completely sequenced using the ABI Big Dye

Terminator kit (P.E. Biosystem). See, SEQ.ID.NO.:3. The putative amino acid sequence for RUP8 is set forth in SEQ.ID.NO.:4. The sequence of RUP9 clones isolated from human genomic DNA matched with the sequence obtained from data base.

c. hRUP10 (Seq. Id. Nos. 5 & 6)

5 The disclosed human RUP10 was identified based upon the use of GenBank database information. While searching the database, a cDNA clone with accession number AC008754 was identified as a human genomic sequence from chromosome 19. The full length RUP10 was cloned by RT-PCR using primers:
5'-CCATGGGGAACGATTCTGTCAGCTACG-3' (SEQ.ID.NO.:45; sense) and
10 5'-GCTATGCCTGAAGCCAGTCTTGTG-3' (SEQ.ID.NO.:46; antisense)
and human leukocyte Marathon-Ready cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech) was used for the amplification in a 50 μ l reaction by the following cycle with step 2 to step 4 repeated 35 times: 94°C for 30 seconds; 94°C for 10 seconds; 62°C for 20 seconds; 72°C for 1.5 minutes; 72°C for 7 minutes. A 1.0
15 Kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem). The nucleic acid sequence of the novel human receptor RUP10 is set forth in SEQ.ID.NO.:5 and the putative amino acid sequence thereof is set forth in SEQ.ID.NO.:6.

20

d. hRUP11 (Seq. Id. Nos. 7 & 8)

The disclosed human RUP11 was identified based upon the use of GenBank database information. While searching the database, a cDNA clone with accession number AC013396 was identified as a human genomic sequence from chromosome 2.

The full length RUP11 was cloned by PCR using primers:

5'-CCAGGATGTTGTGTCACCGTGGTGGC-3' (SEQ.ID.NO.:47; sense),

5'-CACAGCGCTGCAGCCCTGCAGCTGGC-3' (SEQ.ID.NO.:48; antisense)

and human genomic DNA (Clontech) as a template. TaqPlus Precision DNA

5 polymerase (Stratagene) was used for the amplification in a 50µl reaction by the

following cycle with step 2 to step 4 repeated 35 times: 94°C for 3 minutes; 94°C for 20

seconds; 67°C for 20 seconds; 72°C for 1.5 minutes; 72°C for 7 minutes. A 1.3 Kb PCR

fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and

completely sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem). The

10 nucleic acid sequence of the novel human receptor RUP11 is set forth in SEQ.ID.NO.:7

and the putative amino acid sequence thereof is set forth in SEQ.ID.NO.:8.

e. hRUP12 (Seq. Id. Nos. 9 & 10)

The disclosed human RUP12 was identified based upon the use of GenBank database. While searching the database, a cDNA clone with accession number 15 AP000808 was identified to encode a new GPCR, having significant homology with rat RTA and human mas1 oncogene GPCRs. The full length RUP12 was cloned by PCR using primers:

5'-CTTCCTCTCGTAGGGATGAACCAGAC-3' (SEQ.ID.NO.:49; sense)

5'-CTCGCACAGGTGGGAAGCACCTGTGG-3' (SEQ.ID.NO.:50; antisense)

20 and human genomic DNA (Clontech) as template. TaqPlus Precision DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 94°C for 3 min; 94°C for 20 sec; 65°C for 20sec; 72°C for 2 min and 72°C for 7 min. A 1.0kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator kit

(P.E. Biosystem) (see, SEQ.ID.NO.:9 for nucleic acid sequence and SEQ.ID.NO.:10 for deduced amino acid sequence).

f. hRUP13 (Seq. Id. Nos. 11 & 12)

The disclosed human RUP13 was identified based upon the use of GenBank database. While searching the database, a cDNA clone with accession number AC011780 was identified to encode a new GPCR, having significant homology with GPCR fish GPRX-ORYLA. The full length RUP13 was cloned by PCR using primers: 5'-GCCTGTGACAGGAGGTACCTGG-3' (SEQ.ID.NO.:51; sense) 5'-CATATCCCTCCGAGTGTCCAGCGGC-3' (SEQ.ID.NO.:52; antisense) and human genomic DNA (Clontech) as template. TaqPlus Precision DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 94°C for 3 min; 94°C for 20 sec; 65°C for 20sec; 72°C for 2 min and 72°C for 7 min. A 1.35kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem) (see, SEQ.ID.NO.:11 for nucleic acid sequence and SEQ.ID.NO.:12 for deduced amino acid sequence).

g. hRUP14 (Seq. Id. Nos. 13 & 14)

The disclosed human RUP14 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AL137118 was identified as a human genomic sequence from chromosome 13. The full length RUP14 was cloned by PCR using primers: 5'-GCATGGAGAGAAAATTATGTCCTTGCAACC-3' (SEQ.ID.NO.:53; sense) 5'-CAAGAACAGGTCTCATCTAAGAGCTCC-3' (SEQ.ID.NO.:54; antisense) and human genomic DNA (Promega) as a template. Taq Plus Precision polymerase (Stratagene) and 5% DMSO were used for the amplification by the following cycle

with step 2 and step 3 repeated 35 times: 94°C for 3 minute; 94°C for 20 seconds; 58°C for 2 minutes; 72°C for 10 minutes.

A 1.1 Kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem) (see, SEQ.ID.NO.:13 for nucleic acid sequence and SEQ.ID.NO.:14 for deduced amino acid sequence). The sequence of RUP14 clones isolated from human genomic DNA matched with the sequence obtained from database.

h. hRUP15 (Seq. Id. Nos. 15 & 16)

The disclosed human RUP15 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC016468 was identified as a human genomic sequence. The full length RUP15 was cloned by PCR using primers:

5'-GCTGTTGCCATGACGTCCACCTGCAC-3' (SEQ.ID.NO.:55; sense)

5'-GGACAGTTCAAGGTTGCCTAGAAC-3' (SEQ.ID.NO.:56; antisense)

and human genomic DNA (Promega) as a template. Taq Plus Precision polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to 4 repeated 35 times: 94°C for 3 minute; 94°C for 20 seconds; 65°C for 20 seconds; 72°C for 2 minutes and 72°C for 7 minutes.

A 1.5 Kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem). See, SEQ.ID.NO.:15 for nucleic acid sequence and SEQ.ID.NO.:16 for deduced amino acid sequence. The sequence of RUP15 clones isolated from human genomic DNA matched with the sequence obtained from database.

i. hRUP16 (Seq. Id. Nos. 17 & 18)

The disclosed human RUP16 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AL136106 was identified as a human genomic sequence from chromosome 13. The full length RUP16 was cloned by PCR using primers:

5 5'-CTTCGATACTGCTCCTATGCTC-3' (SEQ.ID.NO.:57; sense, 5' of initiation codon),
5'-GTAGTCCACTGAAAGTCCAGTGATCC-3' (SEQ.ID.NO.:58; antisense, 3' of stop codon)
and human skeletal muscle Marathon-Ready cDNA (Clontech) as template. Advantage cDNA polymerase (Clontech) was used for the amplification in a 50ul reaction by the following cycle with step 2 to 4 repeated 35 times: 94°C for 30 seconds; 94°C for 5
10 seconds; 69°C for 15 seconds; 72°C for 1 minute and 72°C for 5 minutes.

A 1.1 Kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the T7 sequenase kit (Amsham). See, SEQ.ID.NO.:17 for nucleic acid sequence and SEQ.ID.NO.:18 for deduced amino acid sequence. The sequence of RUP16 clones matched with four unordered segments of 15 AL136106, indicating that the RUP16 cDNA is composed of 4 exons.

j. hRUP17 (Seq. Id. Nos. 19 & 20)

The disclosed human RUP17 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC023078 was identified as a human genomic sequence from chromosome 20 11. The full length RUP17 was cloned by PCR using primers:
5'-TTTCTGAGCATGGATCCAACCATCTC-3' (SEQ.ID.NO.:59; sense, containing initiation codon)
5'-CTGTCTGACAGGGCAGAGGCTCTTC-3' (SEQ.ID.NO.:60; antisense, 3' of stop codon)
and human genomic DNA (Promega) as template. Advantage cDNA polymerase mix 25 (Clontech) was used for the amplification in a 100ul reaction with 5% DMSO by the

following cycle with step 2 to 4 repeated 30 times: 94°C for 1 min; 94°C for 15 sec; 67°C for 20 sec; 72°C for 1 min and 30 sec; and 72°C for 5 min.

A 970bp PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye 5 Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:19 for nucleic acid sequence and SEQ.ID.NO.:20 for deduced amino acid sequence.

k. hRUP18 (Seq. Id. Nos. 21 & 22)

The disclosed human RUP18 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession 10 Number AC008547 was identified as a human genomic sequence from chromosome 5. The full length RUP18 was cloned by PCR using primers:

5'-GGAACTCGTATAGACCCAGCGTCGCTCC-3' (SEQ.ID.NO.:61; sense, 5' of the initiation codon),
5'-GGAGGTTGCGCCTTAGCGACAGATGACC-3' (SEQ.ID.NO.:62; antisense, 3' of stop 15 codon)

and human genomic DNA (Promega) as template. TaqPlus precision DNA polymerase (Stratagene) was used for the amplification in a 100ul reaction with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 95°C for 5 min; 95°C for 30 sec; 65°C for 30 sec; 72°C for 2 min; and 72°C for 5 min.

20 A 1.3kb PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:21 for nucleic acid sequence and SEQ.ID.NO.:22 for deduced amino acid sequence.

l. hRUP19 (Seq. Id. Nos. 23 & 24)

The disclosed human RUP19 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC026331 was identified as a human genomic sequence from chromosome 12. The full length RUP19 was cloned by PCR using primers:

5 5'-CTGCACCCGGACACTTGCTCTG-3' (SEQ.ID.NO.:63; sense, 5' of initiation codon),
5'-GTCTGCTTGTTCAGTGCCACTAAC-3' (SEQ.ID.NO.:64; antisense, containing the stop codon)

10 and human genomic DNA (Promega) as template. TaqPlus Precision DNA polymerase (Stratagene) was used for the amplification with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 1 min; 94°C for 15 sec; 70°C for 20 sec; 72°C for 1 min and 30 sec; and 72°C for 5 min.

A 1.1kp PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:23 for nucleic acid sequence and SEQ.ID.NO.:24 for deduced amino acid sequence.

m. hRUP20 (Seq. Id. Nos. 25 & 26)

The disclosed human RUP20 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AL161458 was identified as a human genomic sequence from chromosome 1. The full length RUP20 was cloned by PCR using primers:

20 5'-TATCTGCAATTCTATTCTAGCTCCTG-3' (SEQ.ID.NO.:65; sense, 5' of initiation codon),
5'-TGTCCCTAATAAAGTCACATGAATGC-3' (SEQ.ID.NO.:66; antisense, 3' of stop codon)

and human genomic DNA (Promega) as template. Advantage cDNA polymerase mix (Clontech) was used for the amplification with 5% DMSO by the following cycle with

step 2 to 4 repeated 35 times: 94°C for 1 min; 94°C for 15 sec; 60°C for 20 sec; 72°C

for 1 min and 30 sec; and 72°C for 5 min.

A 1.0 kp PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye 5 Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:25 for nucleic acid sequence and SEQ.ID.NO.:26 for deduced amino acid sequence.

n. hRUP21 (Seq. Id. Nos. 27 & 28)

The disclosed human RUP21 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession 10 Number AC026756 was identified as a human genomic sequence from chromosome 13. The full length RUP21 was cloned by PCR using primers:

5'-GGAGACAACCATGAATGAGCCAC-3' (SEQ.ID.NO.:67; sense)

5'-TATTCAAGGGTTGTTGAGAAC-3' (SEQ.ID.NO.:68; antisense)

and human genomic DNA (Promega) as template. Taq Plus Precision polymerase 15 (Stratagene) was used for the amplification in a 100ul reaction with 5% DMSO by the following cycle with step 2 to 4 repeated 30 times: 94°C for 1 min; 94°C for 15 sec; 55°C for 20 sec; 72°C for 1 min and 30 sec; and 72°C for 5 min.

A 1,014 bp PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye 20 Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:27 for nucleic acid sequence and SEQ.ID.NO.:28 for deduced amino acid sequence.

o. hRUP22 (Seq. Id. Nos. 29 & 30)

The disclosed human RUP22 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession

Number AC027026 was identified as a human genomic sequence from chromosome

11. The full length RUP22 was cloned by PCR using primers:

5'-GGCACCAGTGGAGGTTTCTGAGCATG-3' (SEQ.ID.NO.:69; sense, containing

initiation codon)

5 5'-CTGATGGAAGTAGAGGCTGTCCATCTC-3' (SEQ.ID.NO.:70; antisense, 3' of stop codon)

and human genomic DNA (Promega) as template. TaqPlus Precision DNA polymerase (Stratagene) was used for the amplification in a 100ul reaction with 5% DMSO by the following cycle with step 2 to 4 repeated 30 times: 94°C, 1 minutes 94°C, 15 seconds 10 55°C, 20 seconds 72°C, 1.5 minute 72°C, 5 minutes.

A 970bp PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator Kit (P.E. Biosystem). See, SEQ.ID.NO.:29 for nucleic acid sequence and SEQ.ID.NO.:30 for deduced amino acid sequence.

15 p. hRUP23 (Seq. Id. Nos. 31 & 32)

The disclosed human RUP23 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC007104 was identified as a human genomic sequence from chromosome

4. The full length RUP23 was cloned by PCR using primers:

20 5'-CCTGGCGAGCCGCTAGCGCCATG-3' (SEQ.ID.NO.:71; sense, ATG as the initiation codon),

5'-ATGAGCCCTGCCAGGCCCTCAGT-3' (SEQ.ID.NO.:72; antisense, TCA as the stop codon)

and human placenta Marathon-Ready cDNA (Clontech) as template. Advantage cDNA polymerase (Clontech) was used for the amplification in a 50ul reaction by the following

cycle with step 2 to 4 repeated 35 times: 95°C for 30 sec; 95°C for 15 sec; 66°C for 20 sec; 72°C for 1 min and 20 sec; and 72°C for 5 min.

A 1.0 kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:31 for nucleic acid sequence and SEQ.ID.NO.:32 for deduced amino acid sequence.

q. hRUP24 (Seq. Id. Nos. 33 & 34)

The disclosed human RUP25 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession 10 Number AC026331 was identified as a human genomic sequence from chromosome 12. The full length RUP25 was cloned by PCR using primers:

5'-GCTGGAGCATTCACTAGGCGAG-3' (SEQ.ID.NO.:73; sense, 5' of initiation codon),
5'-AGATCCTGGTTCTGGTGACAATG-3' (SEQ.ID.NO.:74; antisense, 3' of stop codon)
and human genomic DNA (Promega) as template. Advantage cDNA polymerase mix 15 (Clontech) was used for the amplification with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 1 minute; 94°C for 15 seconds; 56°C for 20 seconds 72°C for 1 minute 30 seconds and 72°C for 5 minutes.

A 1.2kb PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye 20 Terminator Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:33 for nucleic acid sequence and SEQ.ID.NO.:34 for deduced amino acid sequence.

r. hRUP25 (Seq. Id. Nos. 35 & 36)

The disclosed human RUP25 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession

Number AC026331 was identified as a human genomic sequence from chromosome

12. The full length RUP25 was cloned by PCR using primers:

5'-GCTGGAGCATTCACTAGGCGAG-3' (SEQ.ID.NO.:75; sense, 5' of initiation codon),

5'-AGATCCTGGTTCTGGTGACAATG-3' (SEQ.ID.NO.:76; antisense, 3' of stop codon)

5 and human genomic DNA (Promega) as template. Advantage cDNA polymerase mix (Clontech) was used for the amplification with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 1 minute; 94°C for 15 seconds; 56°C for 20 seconds 72°C for 1 minute 30 seconds and 72°C for 5 minutes.

A 1.2kb PCR fragment was isolated from 1% agarose gel and cloned into the 10 pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:35 for nucleic acid sequence and SEQ.ID.NO.:36 for deduced amino acid sequence.

s. hRUP26 (Seq. Id. Nos. 37 & 38)

The disclosed human RUP26 was identified based upon the use of GeneBank 15 database information. While searching the database, a cDNA clone with Accession Number AC023040 was identified as a human genomic sequence from chromosome

2. The full length RUP26 was cloned by RT-PCR using RUP26 specific primers:

5'-AGCCATCCCTGCCAGGAAGCATGG-3' (SEQ.ID.NO.:77; sense, containing initiation 20 codon)

5'-CCAGACTGTGGACTCAAGAACTTAGG-3' (SEQ.ID.NO.:78; antisense, containing stop 25 codon)

and human pancreas Marathon - Ready cDNA (Clontech) as template. Advantage cDNA polymerase mix (Clontech) was used for the amplification in a 100μl reaction with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 5 minute; 95°C for 30 seconds; 65°C for 30 seconds 72°C for 2 minute and 72°C for 5 minutes.

A 1.1kb PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:37 for nucleic acid sequence and SEQ.ID.NO.:38 for deduced amino acid sequence.

5 t. hRUP27 (Seq. Id. Nos. 39 & 40)

The disclosed human RUP27 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC027643 was identified as a human genomic sequence from chromosome 12. The full length RUP27 was cloned by PCR using RUP27 specific primers:
10 5'-AGTCCACGAACAATGAATCCATTTCATG-3' (SEQ.ID.NO.:79; sense, containing initiation codon),
5'-ATCATGTCTAGACTCATGGTGATCC-3' (SEQ.ID.NO.:80; antisense, 3' of stop codon) and the human adult brain Marathon-Ready cDNA (Clontech) as template. Advantage cDNA polymerase mix (Clontech) was used for the amplification in a 50µl reaction with 5%
15 DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 1 minute; 94°C for 10 seconds; 58°C for 20 seconds 72°C for 1 minute 30 seconds and 72°C for 5 minutes.

A 1.1kb PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye 20 Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:35 for nucleic acid sequence and SEQ.ID.NO.:36 for deduced amino acid sequence. The sequence of RUP27 cDNA clone isolated from human brain was determined to match with five unordered segments of AC027643, indicating that the RUP27 cDNA is composed of 5 exons.

Example 2**PREPARATION OF NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED GPCRS**

Those skilled in the art are credited with the ability to select techniques for mutation of a nucleic acid sequence. Presented below are approaches utilized to 5 create non-endogenous versions of several of the human GPCRs disclosed above. The mutations disclosed below are based upon an algorithmic approach whereby the 16th amino acid (located in the IC3 region of the GPCR) from a conserved proline (or an endogenous, conservative substitution therefore) residue (located in the TM6 region of the GPCR, near the TM6/IC3 interface) is mutated, preferably to an alanine, 10 histidine, arginine or lysine amino acid residue, most preferably to a lysine amino acid residue.

1. Transformer Site-Directed™ Mutagenesis

Preparation of non-endogenous human GPCRs may be accomplished on human GPCRs using Transformer Site-Directed™ Mutagenesis Kit (Clontech) according to the 15 manufacturer instructions. Two mutagenesis primers are utilized, most preferably a lysine mutagenesis oligonucleotide that creates the lysine mutation, and a selection marker oligonucleotide. For convenience, the codon mutation to be incorporated into the human GPCR is also noted, in standard form (Table D):

20

TABLE D

Receptor Identifier	Codon Mutation
hRUP8	V274K
hRUP9	T249K
hRUP10	R232K
hRUP11	M294K
hRUP12	F220K
hRUP16	A238K

hRUP17	Y215K
hRUP18	L294K
hRUP19	T219K
hRUP20	K248A K248H K248R
hRUP21	R240K
hRUP22	Y222K
hRUP24	A245K
hRUP25	I230K
hRUP26	V285K
hRUP27	T248K

2. QuikChange™ Site-Directed™ Mutagenesis

Preparation of non-endogenous human GPCRs can also be accomplished by
5 using QuikChange™ Site-Directed™ Mutagenesis Kit (Stratagene, according to manufacturer's instructions). Endogenous GPCR is preferably used as a template and two mutagenesis primers utilized, as well as, most preferably, a lysine mutagenesis oligonucleotide and a selection marker oligonucleotide (included in kit). For convenience, the codon mutation incorporated into the novel human GPCR and the
10 respective oligonucleotides are noted, in standard form (Table E):

TABLE E

Receptor Identifier	Codon Mutation	5'-3' orientation (sense), (SEQ.ID.NO.) mutation <u>underlined</u>	5'-3' orientation (antisense) (SEQ.ID.NO.)	Cycle Conditions Min ('), Sec (") Cycles 2-4 repeated 16 times
hRUP13	A268K	GGGGAGGGAAAGCAA <u>AGGTGGTCCTCCTGG</u> (81)	CCAGGAGAACCAC <u>TTGCTTCCCTCCCC</u> (82)	98° for 2' 98° for 30" 56°C for 30" 72° for 11' 40" 72° for 5'
hRUP14	L246K	CAGGAAGGCAAAGAC CACCATCATCATC (85)	GATGATGATGGTGGT <u>CTTGCCTCCTG</u> (86)	98° for 2' 98° for 30" 55°C for 30" 72° for 11' 40" 72° for 5'

hRUP15	A398K	CCAGTGCAAAGCTAAG AAAGTGATCTTC (89)	GAAGATCACTTTCTTA GCTTGCCTGG (90)	98° for 2' 98° for 30" 55°C for 30" 72° for 11' 40" 72° for 5'
hRUP23	W275K	GCCGCCACCGCGGCCAA <u>GAGGAAGATTGGC (93)</u>	GCCAATCTTCCTCTTG GCGCGGTGGCGGC (94)	98° for 2' 98° for 30" 56°C for 30" 72° for 11' 40" 72° for 5'

The non-endogenous human GPCRs were then sequenced and the derived and verified nucleic acid and amino acid sequences are listed in the accompanying 5 "Sequence Listing" appendix to this patent document, as summarized in Table F below:

TABLE F

Non Endogenous Human GPCR	Nucleic Acid Sequence Listing	Amino Acid Sequence Listing
hRUP13	SEQ.ID.NO.:83	SEQ.ID.NO.:84
hRUP14	SEQ.ID.NO.:87	SEQ.ID.NO.:88
hRUP15	SEQ.ID.NO.:91	SEQ.ID.NO.:92
hRUP23	SEQ.ID.NO.:95	SEQ.ID.NO.:96

10 **Example 3**
RECEPTOR EXPRESSION

Although a variety of cells are available to the art for the expression of proteins, it is most preferred that mammalian cells be utilized. The primary reason for this is predicated upon practicalities, *i.e.*, utilization of, *e.g.*, yeast cells for the 15 expression of a GPCR, while possible, introduces into the protocol a non-mammalian cell which may not (indeed, in the case of yeast, does not) include the receptor-coupling, genetic-mechanism and secretary pathways that have evolved for mammalian systems – thus, results obtained in non-mammalian cells, while of

potential use, are not as preferred as that obtained from mammalian cells. Of the mammalian cells, COS-7, 293 and 293T cells are particularly preferred, although the specific mammalian cell utilized can be predicated upon the particular needs of the artisan.

5 **a. Transient Transfection**

On day one, 6×10^6 / 10 cm dish of 293 cells well were plated out. On day two, two reaction tubes were prepared (the proportions to follow for each tube are per plate): tube A was prepared by mixing 4 μ g DNA (e.g., pCMV vector; pCMV vector with receptor cDNA, etc.) in 0.5 ml serum free DMEM (Gibco BRL); tube B was prepared by 10 mixing 24 μ l lipofectamine (Gibco BRL) in 0.5ml serum free DMEM. Tubes A and B were admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated 293 cells were washed with 1XPBS, followed by addition of 5 ml serum free DMEM. 1 ml of the transfaction mixture were added to the cells, followed by incubation for 4hrs at 15 37°C/5% CO₂. The transfaction mixture was removed by aspiration, followed by the addition of 10ml of DMEM/10% Fetal Bovine Serum. Cells were incubated at 37°C/5% CO₂. After 48hr incubation, cells were harvested and utilized for analysis.

b. Stable Cell Lines: Gs Fusion Protein

Approximately 12 $\times 10^6$ 293 cells are plated on a 15cm tissue culture plate. 20 Grown in DME High Glucose Medium containing ten percent fetal bovine serum and one percent sodium pyruvate, L-glutamine, and anti-biotics. Twenty-four hours following plating of 293 cells to ~80% confluency, the cells are transfected using 12 μ g of DNA. The 12 μ g of DNA is combined with 60ul of lipofectamine and 2mL of DME High Glucose Medium without serum. The medium is aspirated from the plates and the 25 cells are washed once with medium without serum. The DNA, lipofectamine, and

medium mixture is added to the plate along with 10mL of medium without serum. Following incubation at 37 degrees Celsius for four to five hours, the medium is aspirated and 25ml of medium containing serum is added. Twenty-four hours following transfection, the medium is aspirated again, and fresh medium with serum is added.

5 Forty-eight hours following transfection, the medium is aspirated and medium with serum is added containing geneticin (G418 drug) at a final concentration of 500 μ g/mL. The transfected cells now undergo selection for positively transfected cells containing the G418 resistant gene. The medium is replaced every four to five days as selection occurs. During selection, cells are grown to create stable pools, or split for stable clonal

10 selection.

Example 4

**ASSAYS FOR DETERMINATION OF CONSTITUTIVE ACTIVITY
OF NON-ENDOGENOUS GPCRs**

15 A variety of approaches are available for assessment of constitutive activity of the non-endogenous human GPCRs. The following are illustrative; those of ordinary skill in the art are credited with the ability to determine those techniques that are preferentially beneficial for the needs of the artisan.

20 **1. Membrane Binding Assays: [35 S]GTP γ S Assay**

When a G protein-coupled receptor is in its active state, either as a result of ligand binding or constitutive activation, the receptor couples to a G protein and stimulates the release of GDP and subsequent binding of GTP to the G protein. The alpha subunit of the G protein-receptor complex acts as a GTPase and slowly hydrolyzes the GTP to GDP, at which point the receptor normally is deactivated. Constitutively activated receptors continue to exchange GDP for GTP. The non-hydrolyzable GTP analog, [35 S]GTP γ S, can be utilized to demonstrate enhanced binding of [35 S]GTP γ S to membranes expressing constitutively activated receptors. The advantage of using

[³⁵S]GTP γ S binding to measure constitutive activation is that: (a) it is generically applicable to all G protein-coupled receptors; (b) it is proximal at the membrane surface making it less likely to pick-up molecules which affect the intracellular cascade.

The assay utilizes the ability of G protein coupled receptors to stimulate
5 [³⁵S]GTP γ S binding to membranes expressing the relevant receptors. The assay can, therefore, be used in the direct identification method to screen candidate compounds to known, orphan and constitutively activated G protein-coupled receptors. The assay is generic and has application to drug discovery at all G protein-coupled receptors.

The [³⁵S]GTP γ S assay was incubated in 20 mM HEPES and between 1 and
10 about 20mM MgCl₂ (this amount can be adjusted for optimization of results, although 20mM is preferred) pH 7.4, binding buffer with between about 0.3 and about 1.2 nM [³⁵S]GTP γ S (this amount can be adjusted for optimization of results, although 1.2 is preferred) and 12.5 to 75 μ g membrane protein (e.g. 293 cells expressing the Gs Fusion Protein; this amount can be adjusted for optimization) and 10 μ M GDP (this amount can
15 be changed for optimization) for 1 hour. Wheatgerm agglutinin beads (25 μ l; Amersham) were then added and the mixture incubated for another 30 minutes at room temperature. The tubes were then centrifuged at 1500 x g for 5 minutes at room temperature and then counted in a scintillation counter.

2. Adenylyl Cyclase

20 A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays can be modified for use with crude plasma membranes. The Flash Plate wells can contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP

antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors.

Transfected cells were harvested approximately twenty four hours after transient transfection. Media is carefully aspirated off and discarded. 10ml of PBS is gently 5 added to each dish of cells followed by careful aspiration. 1ml of Sigma cell dissociation buffer and 3ml of PBS are added to each plate. Cells were pipeted off the plate and the cell suspension was collected into a 50ml conical centrifuge tube. Cells were then centrifuged at room temperature at 1,100 rpm for 5 min. The cell pellet was carefully re-suspended into an appropriate volume of PBS (about 3ml/plate). The cells 10 were then counted using a hemocytometer and additional PBS was added to give the appropriate number of cells (with a final volume of about 50 μ l/well).

cAMP standards and Detection Buffer (comprising 1 μ Ci of tracer [125 I cAMP (50 μ l] to 11 ml Detection Buffer) was prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer was prepared fresh for screening and 15 contained 50 μ l of Stimulation Buffer, 3 μ l of test compound (12uM final assay concentration) and 50 μ l cells, Assay Buffer was stored on ice until utilized. The assay was initiated by addition of 50 μ l of cAMP standards to appropriate wells followed by addition of 50ul of PBSA to wells H-11 and H12. 50 μ l of Stimulation Buffer was added to all wells. DMSO (or selected candidate compounds) was added to appropriate wells 20 using a pin tool capable of dispensing 3 μ l of compound solution, with a final assay concentration of 12 μ M test compound and 100 μ l total assay volume. The cells were then added to the wells and incubated for 60 min at room temperature. 100 μ l of Detection Mix containing tracer cAMP was then added to the wells. Plates were then incubated additional 2 hours followed by counting in a Wallac MicroBeta scintillation

counter. Values of cAMP/well were then extrapolated from a standard cAMP curve which was contained within each assay plate.

3. Cell-Based cAMP for Gi Coupled Target GPCRs

5 TSHR is a Gs coupled GPCR that causes the accumulation of cAMP upon activation. TSHR will be constitutively activated by mutating amino acid residue 623 (*i.e.*, changing an alanine residue to an isoleucine residue). A Gi coupled receptor is expected to inhibit adenylyl cyclase, and, therefore, decrease the level of cAMP production, which can make assessment of cAMP levels challenging. An effective 10 technique for measuring the decrease in production of cAMP as an indication of constitutive activation of a Gi coupled receptor can be accomplished by co-transfected, most preferably, non-endogenous, constitutively activated TSHR (TSHR-A623I) (or an endogenous, constitutively active Gs coupled receptor) as a "signal enhancer" with a Gi linked target GPCR to establish a baseline level of cAMP. Upon creating a non- 15 endogenous version of the Gi coupled receptor, this non-endogenous version of the target GPCR is then co-transfected with the signal enhancer, and it is this material that can be used for screening. We will utilize such approach to effectively generate a signal when a cAMP assay is used; this approach is preferably used in the direct identification of candidate compounds against Gi coupled receptors. It is noted that for a Gi coupled 20 GPCR, when this approach is used, an inverse agonist of the target GPCR will increase the cAMP signal and an agonist will decrease the cAMP signal.

On day one, 2×10^4 293 and 293 cells/well will be plated out. On day two, two reaction tubes will be prepared (the proportions to follow for each tube are per plate): tube A will be prepared by mixing 2 μ g DNA of each receptor transfected into the 25 mammalian cells, for a total of 4 μ g DNA (*e.g.*, pCMV vector, pCMV vector with mutated TSHR (TSHR-A623I); TSHR-A623I and GPCR, etc.) in 1.2ml serum free

DMEM (Irvine Scientific, Irvine, CA); tube B will be prepared by mixing 120 μ l lipofectamine (Gibco BRL) in 1.2ml serum free DMEM. Tubes A and B will then be admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated 293 cells 5 will be washed with 1XPBS, followed by addition of 10ml serum free DMEM. 2.4ml of the transfection mixture will then be added to the cells, followed by incubation for 4hrs at 37°C/5% CO₂. The transfection mixture will then be removed by aspiration, followed by the addition of 25ml of DMEM/10% Fetal Bovine Serum. Cells will then be 10 incubated at 37°C/5% CO₂. After 24hr incubation, cells will then be harvested and utilized for analysis.

A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) is designed for cell-based assays, however, can be modified for use with crude plasma membranes depending on the need of the skilled artisan. The Flash Plate wells will contain a scintillant coating which also contains a specific antibody 15 recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors.

Transfected cells will be harvested approximately twenty four hours after 20 transient transfection. Media will be carefully aspirated off and discarded. 10ml of PBS will be gently added to each dish of cells followed by careful aspiration. 1ml of Sigma cell dissociation buffer and 3ml of PBS will be added to each plate. Cells will be pipeted off the plate and the cell suspension will be collected into a 50ml conical centrifuge tube. Cells will then be centrifuged at room temperature at 1,100 rpm for 5 min. The cell 25 pellet will be carefully re-suspended into an appropriate volume of PBS (about

3ml/plate). The cells will then be counted using a hemocytometer and additional PBS is added to give the appropriate number of cells (with a final volume of about 50 μ l/well).

cAMP standards and Detection Buffer (comprising 1 μ Ci of tracer [125 I cAMP 5 (50 μ l] to 11 ml Detection Buffer) will be prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer should be prepared fresh for screening and contained 50 μ l of Stimulation Buffer, 3 μ l of test compound (12uM final assay concentration) and 50 μ l cells, Assay Buffer can be stored on ice until utilized. The assay can be initiated by addition of 50 μ l of cAMP standards to appropriate wells followed by 10 addition of 50 μ l of PBSA to wells H-11 and H12. 50 μ l of Stimulation Buffer will be added to all wells. Selected compounds (e.g., TSH) will be added to appropriate wells using a pin tool capable of dispensing 3 μ l of compound solution, with a final assay concentration of 12 μ M test compound and 100 μ l total assay volume. The cells will then be added to the wells and incubated for 60 min at room temperature. 100 μ l of Detection 15 Mix containing tracer cAMP will then be added to the wells. Plates were then incubated additional 2 hours followed by counting in a Wallac MicroBeta scintillation counter. Values of cAMP/well will then be extrapolated from a standard cAMP curve which is contained within each assay plate.

4. Reporter-Based Assays

20 a. CRE-LUC Reporter Assay (Gs-associated receptors)

293 and 293T cells are plated-out on 96 well plates at a density of 2×10^4 cells per well and were transfected using Lipofectamine Reagent (BRL) the following day according to manufacturer instructions. A DNA/lipid mixture is prepared for each 6-well transfection as follows: 260ng of plasmid DNA in 100 μ l of DMEM were gently 25 mixed with 2 μ l of lipid in 100 μ l of DMEM (the 260ng of plasmid DNA consisted of

200ng of a 8xCRE-Luc reporter plasmid, 50ng of pCMV comprising endogenous receptor or non-endogenous receptor or pCMV alone, and 10ng of a GPRS expression plasmid (GPRS in pcDNA3 (Invitrogen)). The 8XCRE-Luc reporter plasmid was prepared as follows: vector SRIF- β -gal was obtained by cloning the rat somatostatin promoter (-71/+51) at BglIV-HindIII site in the p β gal-Basic Vector (Clontech). Eight (8) copies of cAMP response element were obtained by PCR from an adenovirus template AdpCF126CCRE8 (see, 7 *Human Gene Therapy* 1883 (1996)) and cloned into the SRIF- β -gal vector at the Kpn-BglIV site, resulting in the 8xCRE- β -gal reporter vector. The 8xCRE-Luc reporter plasmid was generated by replacing the beta-galactosidase gene in the 8xCRE- β -gal reporter vector with the luciferase gene obtained from the pGL3-basic vector (Promega) at the HindIII-BamHI site. Following 30 min. incubation at room temperature, the DNA/lipid mixture was diluted with 400 μ l of DMEM and 100 μ l of the diluted mixture was added to each well. 100 μ l of DMEM with 10% FCS were added to each well after a 4hr incubation in a cell culture incubator. The following day the transfected cells were changed with 200 μ l/well of DMEM with 10% FCS. Eight (8) hours later, the wells were changed to 100 μ l /well of DMEM without phenol red, after one wash with PBS. Luciferase activity were measured the next day using the LucLiteTM reporter gene assay kit (Packard) following manufacturer instructions and read on a 1450 MicroBetaTM 20 scintillation and luminescence counter (Wallac).

b. AP1 reporter assay (Gq-associated receptors)

A method to detect Gq stimulation depends on the known property of Gq-dependent phospholipase C to cause the activation of genes containing AP1 elements in their promoter. A PathdetectTM AP-1 cis-Reporting System (Stratagene, Catalogue # 219073) can be utilized following the protocol set forth above with respect to the

CREB reporter assay, except that the components of the calcium phosphate precipitate were 410 ng pAP1-Luc, 80 ng pCMV-receptor expression plasmid, and 20 ng CMV-SEAP.

c. **SRF-LUC Reporter Assay (Gq- associated receptors)**

5 One method to detect Gq stimulation depends on the known property of Gq-dependent phospholipase C to cause the activation of genes containing serum response factors in their promoter. A Pathdetect™ SRF-Luc-Reporting System (Stratagene) can be utilized to assay for Gq coupled activity in, e.g., COS7 cells. Cells are transfected with the plasmid components of the system and the indicated
10 expression plasmid encoding endogenous or non-endogenous GPCR using a Mammalian Transfection™ Kit (Stratagene, Catalogue #200285) according to the manufacturer's instructions. Briefly, 410 ng SRF-Luc, 80 ng pCMV-receptor expression plasmid and 20 ng CMV-SEAP (secreted alkaline phosphatase expression plasmid; alkaline phosphatase activity is measured in the media of transfected cells to
15 control for variations in transfection efficiency between samples) are combined in a calcium phosphate precipitate as per the manufacturer's instructions. Half of the precipitate is equally distributed over 3 wells in a 96-well plate, kept on the cells in a serum free media for 24 hours. The last 5 hours the cells are incubated with 1 μ M Angiotensin, where indicated. Cells are then lysed and assayed for luciferase activity
20 using a Luclite™ Kit (Packard, Cat. # 6016911) and "Trilux 1450 Microbeta" liquid scintillation and luminescence counter (Wallac) as per the manufacturer's instructions. The data can be analyzed using GraphPad Prism™ 2.0a (GraphPad Software Inc.).

d. Intracellular IP₃ Accumulation Assay (Gq-associated receptors)

On day 1, cells comprising the receptors (endogenous and/or non-endogenous) can be plated onto 24 well plates, usually 1x10⁵ cells/well (although this number can be optimized. On day 2 cells can be transfected by firstly mixing 0.25µg DNA in 50 µl serum free DMEM/well and 2 µl lipofectamine in 50 µl serumfree DMEM/well. The solutions are gently mixed and incubated for 15-30 min at room temperature. Cells are washed with 0.5 ml PBS and 400 µl of serum free media is mixed with the transfection media and added to the cells. The cells are then incubated for 3-4 hrs at 37°C/5%CO₂ and then the transfection media is removed and replaced with 1ml/well of regular growth media. On day 3 the cells are labeled with ³H-myo-inositol. Briefly, the media is removed and the cells are washed with 0.5 ml PBS. Then 0.5 ml inositol-free/serum free media (GIBCO BRL) is added/well with 0.25 µCi of ³H-myo-inositol/ well and the cells are incubated for 16-18 hrs o/n at 37°C/5%CO₂. On Day 4 the cells are washed with 0.5 ml PBS and 0.45 ml of assay medium is added containing inositol-free/serum free media 10 µM pargyline 10 mM lithium chloride or 0.4 ml of assay medium and 50µl of 10x ketanserin (ket) to final concentration of 10µM. The cells are then incubated for 30 min at 37°C. The cells are then washed with 0.5 ml PBS and 200µl of fresh/icecold stop solution (1M KOH; 18 mM Na-borate; 3.8 mM EDTA) is added/well. The solution is kept on ice for 5-10 min or until cells were lysed and then neutralized by 200 µl of fresh/ice cold neutralization sol. (7.5 % HCL). The lysate is then transferred into 1.5 ml eppendorf tubes and 1 ml of chloroform/methanol (1:2) is added/tube. The solution is vortexed for 15 sec and the upper phase is applied to a Biorad AG1-X8™ anion exchange resin (100-200 mesh). Firstly, the resin is washed with water at 1:1.25 W/V and 0.9 ml of upper phase is loaded onto the column. The column is washed with 10 mls of 5 mM myo-inositol and 10 ml of 5 mM Na-borate/60mM Na-formate. The inositol

tris phosphates are eluted into scintillation vials containing 10 ml of scintillation cocktail with 2 ml of 0.1 M formic acid/ 1 M ammonium formate. The columns are regenerated by washing with 10 ml of 0.1 M formic acid/3M ammonium formate and rinsed twice with dd H₂O and stored at 4°C in water.

5 Exemplary results are presented below in Table G:

TABLE G

Receptor	Mutation	Assay Utilized Figure No.)	Signal Generated: CMV	Signal Generated: Endogenous Version (Relative Light Units)	Signal Generated: Non-Endogenous Version (Relative Light Units)	Difference (=<>) Between • CMV v. • Wild-type • Wild-type v. Mutant
hRUP12	N/A	IP ₃ (Figure 1)	317.03 cpm/mg protein	3463.29 cpm/mg protein	--	1. 11 Fold =<
hRUP13	N/A	cAMP (Figure 2)	8.06 pmol/cAMP/mg protein	19.10 pmol/cAMP/mg protein	--	1. 2.4 Fold =<
	A268K	8XCRE-LUC (Figure 3)	3665.43 LCPS	83280.17 LCPS	61713.6 LCPS	1. 23 Fold =< 2. 26% <
hRUP14	L246K	8XCRE-LUC (Figure 5)	86.07 LCPS	1962.87 LCPS	789.73 LCPS	1. 23 Fold =< 2. 60% <
hRUP15	A398K	8XCRE-LUC (Figure 6)	86.07 LCPS	18286.77 LCPS	17034.83 LCPS	1. 212 Fold =< 2. 1% <
	A398K	cAMP (Figure 7)	15.00 pmol/cAMP/mg protein	164.4 pmol/cAMP/mg protein	117.5 pmol/cAMP/mg protein	1. 11 Fold =< 2. 29% <
hRUP17	N/A	IP ₃ (Figure 9)	317.03 cpm/mg protein	741.07 cpm/mg protein	--	1. 2.3 Fold =<
hRUP21	N/A	IP ₃ (Figure 10)	730.5 cpm/mg protein	1421.9 cpm/mg protein	--	1. 2 Fold =<
hRUP23	W275K	8XCRE-LUC (Figure 11)	311.73 pmol/cAMP/mg protein	13756.00 pmol/cAMP/mg protein	9756.87 pmol/cAMP/mg protein	1. 44 Fold =< 2. 30% <

N/A = not applied

Exemplary results of GTP γ S assay for detecting constitutive activation, as disclosed in Example 4(1) above, was accomplished utilizing Gs:Fusion Protein Constructs on human RUP13 and RUP15. Table H below lists the signals generated from this assay and the difference in signals as indicated:

5

TABLE H

Receptor: Gs Fusion Protein	Assay Utilized	Signal Generated: CMV (cpm bound GTP)	Signal Generated: Fusion Protein (cpm bound GTP)	Signal Generated: CMV+ 10 μ M GDP (cpm bound GTP)	Signal Generated: Fusion Protein + 10 μ M GDP (cpm bound GTP)	Difference Between: 1. CMV v. Fusion Protein 2. CMV+GDP vs. Fusion+GDP 3. Fusion vs. Fusion+GDP (cpm bound GTP)
hRUP13-Gs	GTP γ S (Figure 4)	32494.0	49351.30	11148.30	28834.67	1. 1.5 Fold \Leftarrow 2. 2.6 Fold \Leftarrow 3. 42% <
hRUP15-Gs	GTP γ S (Figure 8)	30131.67	32493.67	7697.00	14157.33	1. 1.1 Fold \Leftarrow 2. 1.8 Fold \Leftarrow 3. 56% <

Example 5
FUSION PROTEIN PREPARATION

10 a. **GPCR:Gs Fusion Construct**

The design of the constitutively activated GPCR-G protein fusion construct was accomplished as follows: both the 5' and 3' ends of the rat G protein Gs α (long form; Itoh, H. et al., 83 *PNAS* 3776 (1986)) were engineered to include a HindIII (5'-15 AAGCTT-3') sequence thereon. Following confirmation of the correct sequence (including the flanking HindIII sequences), the entire sequence was shuttled into pcDNA3.1(-) (Invitrogen, cat. no. V795-20) by subcloning using the HindIII restriction site of that vector. The correct orientation for the Gs α sequence was determined after

subcloning into pcDNA3.1(-). The modified pcDNA3.1(-) containing the rat G α gene at HindIII sequence was then verified; this vector was now available as a “universal” G α protein vector. The pcDNA3.1(-) vector contains a variety of well-known restriction sites upstream of the HindIII site, thus beneficially providing the ability to 5 insert, upstream of the Gs protein, the coding sequence of an endogenous, constitutively active GPCR. This same approach can be utilized to create other “universal” G protein vectors, and, of course, other commercially available or proprietary vectors known to the artisan can be utilized – the important criteria is that the sequence for the GPCR be upstream and in-frame with that of the G protein.

10 RUP13 couples via Gs. For the following exemplary GPCR Fusion Proteins, fusion to G α was accomplished.

A RUP13-G α Fusion Protein construct was made as follows: primers were designed as follows:

15 5'-gatc[TCTAGAAT]GGAGTCCTCACCCATCCCCAG -3' (SEQ.ID.NO.:97; sense)
5'-gatc[GATATC]CGTGACTCCAGCCGGGTGAGGCAGG-3' (SEQ.ID.NO.:98; antisense).

Nucleotides in lower caps are included as spacers in the restriction sites (designated in brackets) between the G protein and RUP13. The sense and anti-sense primers included the restriction sites for XbaI and EcoRV, respectively, such that spacers (attributed to the restriction sites) exists between the G protein and RUP15.

20 PCR was then utilized to secure the respective receptor sequences for fusion within the G α universal vector disclosed above, using the following protocol for each: 100ng cDNA for RUP15 was added to separate tubes containing 2 μ l of each primer (sense and anti-sense), 3 μ L of 10mM dNTPs, 10 μ L of 10XTaqPlusTM Precision buffer, 1 μ L of TaqPlusTM Precision polymerase (Stratagene: #600211), and 80 μ L of water.

25 Reaction temperatures and cycle times for RUP15 were as follows with cycle steps 2

through 4 were repeated 35 times: 94°C for 1 min; 94°C for 30 seconds; 62°C for 20 sec; 72°C 1 min 40sec; and 72° C 5 min . PCR product for was run on a 1% agarose gel and then purified (data not shown). The purified product was digested with XbaI and EcoRV and the desired inserts purified and ligated into the Gs universal vector at the 5 respective restriction site. The positive clones was isolated following transformation and determined by restriction enzyme digest; expression using 293 cells was accomplished following the protocol set forth *infra*. Each positive clone for RUP15-Gs Fusion Protein was sequenced to verify correctness. (See, SEQ.ID.NO.:99 for nucleic acid sequence and SEQ.ID.NO.:100 for amino acid sequence).

10 RUP15 couples via Gs. For the following exemplary GPCR Fusion Proteins, fusion to Gs α was accomplished.

A RUP15-Gs α Fusion Protein construct was made as follows: primers were designed as follows:

5'-TCTAGAATGACGTCCACCTGCACCAACAGC-3' (SEQ.ID.NO.:101; sense)
15 5'-gatatcGCAGGAAAAGTAGCAGAATCGTAGGAAG-3' (SEQ.ID.NO.:102; antisense).
Nucleotides in lower caps are included as spacers in the restriction sites between the G protein and RUP15. The sense and anti-sense primers included the restriction sites for EcoRV and XbaI, respectively, such that spacers (attributed to the restriction sites) exists between the G protein and RUP15.

20 PCR was then utilized to secure the respective receptor sequences for fusion within the Gs α universal vector disclosed above, using the following protocol for each: 100ng cDNA for RUP15 was added to separate tubes containing 2 μ l of each primer (sense and anti-sense), 3 μ L of 10mM dNTPs, 10 μ L of 10XTaqPlusTM Precision buffer, 1 μ L of TaqPlusTM Precision polymerase (Stratagene: #600211), and 80 μ L of water.

25 Reaction temperatures and cycle times for RUP15 were as follows with cycle steps 2

through 4 were repeated 35 times: 94°C for 1 min; 94°C for 30 seconds; 62°C for 20 sec; 72°C 1 min 40sec; and 72° C 5 min . PCR product for was run on a 1% agarose gel and then purified (data not shown). The purified product was digested). The purified product was digested with EcoRV and Xba1 and the desired inserts purified and 5 ligated into the Gs universal vector at the respective restriction site. The positive clones was isolated following transformation and determined by restriction enzyme digest; expression using 293 cells was accomplished following the protocol set forth *infra*. Each positive clone for RUP15-Gs Fusion Protein was sequenced to verify correctness. (See, SEQ.ID.NO.:103 for nucleic acid sequence and SEQ.ID.NO.:104 for amino acid 10 sequence).

b. Gq(6 amino acid deletion)/Gi Fusion Construct

The design of a Gq (del)/Gi fusion construct can be accomplished as follows: the N-terminal six (6) amino acids (amino acids 2 through 7, having the sequence of TLESIM (SEQ.ID.NO.: 129) Gαq-subunit will be deleted and the C-terminal five (5) 15 amino acids, having the sequence EYNLV (SEQ.ID.NO.:130) will be replace with the corresponding amino acids of the Gαi Protein, having the sequence DCGLF (SEQ.ID.NO.:131). This fusion construct will be obtained by PCR using the following primers:

20 5'-gatcaagcttcCATGGCGTGCTGCCTGAGCGAGGAG-3' (SEQ.ID.NO.:132) and

5'-gatcggtatccTTAGAACAGGCCGAGTCCTTCAGGTTCAGCTGCAGGATGGTG-3'
(SEQ.ID.NO.:133)

and Plasmid 63313 which contains the mouse Gαq-wild type version with a 25 hemagglutinin tag as template. Nucleotides in lower caps are included as spacers.

TaqPlus Precision DNA polymerase (Stratagene) will be utilized for the amplification by the following cycles, with steps 2 through 4 repeated 35 times: 95°C

for 2 min; 95°C for 20 sec; 56°C for 20 sec; 72°C for 2 min; and 72°C for 7 min. The PCR product will be cloned into a pCR_{II}-TOPO vector (Invitrogen) and sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem). Inserts from a TOPO clone containing the sequence of the fusion construct will be shuttled into the expression 5 vector pcDNA3.1(+) at the HindIII/BamHI site by a 2 step cloning process.

Example 6

TISSUE DISTRIBUTION OF THE DISCLOSED HUMAN GPCRs: RT-PCR

RT-PCR was applied to confirm the expression and to determine the tissue 10 distribution of several novel human GPCRs. Oligonucleotides utilized were GPCR-specific and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) were utilized for the amplification in a 40µl reaction according to the manufacturer's instructions. 20µl of the reaction will be loaded on a 1.5% agarose gel to analyze the RT-PCR products. Table J below lists the 15 receptors, the cycle conditions and the primers utilized.

TABLE J

Receptor Identifier	Cycle Conditions Min ('), Sec (") Cycles 2-4 repeated 30 times	5' Primer (SEQ.ID.NO.)	3' Primer (SEQ.ID.NO.)	DNA Fragment	Tissue Expression
hRUP10	94° for 30" 94° for 10" 62°C for 20" 72° for 1' 72° for 7' *cycles 2-4 repeated 35 times	CATGTATGC CAGCGTCCT GCTCC (105)	GCTATGCCTG AAGCCAGTC TTGTG (106)	730bp	Kidney, leukocyte, liver, placenta and spleen
hRUP11	94° for 2' 94° for 15" 67°C for 15" 72° for 45" 72° for 5'	GCACCTGCT CCTGAGCAC CTTCTCC (107)	CACAGCGCT GCAGCCCTG CAGCTGGC (108)	630bp	Liver, kidney, pancreas, colon, small intestinal, spleen and prostate

hRUP12	94° for 2' 94° for 15" 66°C for 15" 72° for 45" 72° for 5'	CCAGTGATG ACTCTGTCC AGCCTG (109)	CAGACACTT GGCAGGGAC GAGGTG (110)	490bp	Brain, colon, heart, kidney, leukocyte, pancreas, prostate, small intestinal, spleen, testis, and thymus
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hRUP13	94° for 1' 94° for 15" 68°C for 20" 72° for 1' 45" 72° for 5'	CTTGTGGTCT ACTGCAGCA TGTCCG (111)	CATATCCCTC CGAGTGTCC AGCGGC (112)	700bp	Placenta and lung
hRUP14	94° for 1' 94° for 15" 68°C for 20" 72° for 1' 45" 72° for 5'	ATGGATCCT TATCATGGC TTCCTC (113)	CAAGAACAG GTCTCATCTA AGAGCTCC (114)	700bp	Not yet determined
hRUP16	94° for 30" 94° for 5" 69°C for 15" 72° for 30" 72° for 5'	CTCTGATGC CATCTGCTG GATTCTG (115)	GTAGTCCACT GAAAGTCCA GTGATCC (116)	370bp	Fetal brain, fetal kidney and fetal skeletal muscle
hRUP18	94° for 2' 94° for 15" 60°C for 20" 72° for 1' 72° for 5'	TGGTGGCGA TGGCCAACA GCGCTC (117)	GTTGCGCCTT AGCGACAGA TGACC (118)	330bp	Pancreas
hRUP21	94° for 1' 94° for 15" 56°C for 20" 72° for 40" *cycles 2-3 repeated 30 times	TCAACCTGT ATAGCAGCA TCCTC (119)	AAGGAGTAG CAGAATGGT TAGCC (120)		Kidney, lung and testis
hRUP22	94° for 30" 94° for 15" 69°C for 20" 72° for 40" *cycles 2-3 repeated 30 times	GACACCTGT CAGCGGTG TGTGTG (121)	CTGATGGAA GTAGAGGCT GTCCATCTC (122)		Testis, thymus and spleen
hRUP23	94° for 2' 94° for 15" 60°C for 20" 72° for 1' 72° for 5'	GCGCTGAGC GCAGACCAG TGGCTG (123)	CACGGTGAC GAAGGGCAC GAGCTC (124)	520bp	Placenta
hRUP26	94° for 2' 94° for 15" 65°C for 20" 72° for 1' 72° for 5'	AGCCATCCC TGCCAGGAA GCATGG (125)	CCAGGTAGG TGTGCAGCA CAATGGC (126)	470bp	Pancreas
hRUP27	94° for 30" 94° for 10" 55°C for 20" 72° for 1' 72° for 3' *cycles 2-4 repeated 35 times	CTGTTCAAC AGGGCTGGT TGGCAAC (127)	ATCATGTCTA GACTCATGGT GATCC (128)	890bp	Brain

Example 7**Protocol: Direct Identification of Inverse Agonists and Agonists****A. [³⁵S]GTPγS Assay**

5 Although we have utilized endogenous, constitutively active GPCRs for the direct identification of candidate compounds as, *e.g.*, inverse agonists, for reasons that are not altogether understood, intra-assay variation can become exacerbated. Preferably, then, a GPCR Fusion Protein, as disclosed above, is also utilized with a non-endogenous, constitutively activated GPCR. We have determined that when such a 10 protein is used, intra-assay variation appears to be substantially stabilized, whereby an effective signal-to-noise ratio is obtained. This has the beneficial result of allowing for a more robust identification of candidate compounds. Thus, it is preferred that for direct identification, a GPCR Fusion Protein be used and that when utilized, the following assay protocols be utilized.

15 **1. Membrane Preparation**

Membranes comprising the constitutively active orphan GPCR Fusion Protein of interest and for use in the direct identification of candidate compounds as inverse agonists, agonists or partial agonists are preferably prepared as follows:

a. Materials

20 “Membrane Scrape Buffer” is comprised of 20mM HEPES and 10mM EDTA, pH 7.4; “Membrane Wash Buffer” is comprised of 20 mM HEPES and 0.1 mM EDTA, pH 7.4; “Binding Buffer” is comprised of 20mM HEPES, 100 mM NaCl, and 10 mM MgCl₂, pH 7.4

b. Procedure

25 All materials will be kept on ice throughout the procedure. Firstly, the media will be aspirated from a confluent monolayer of cells, followed by rinse with 10ml cold

PBS, followed by aspiration. Thereafter, 5ml of Membrane Scrape Buffer will be added to scrape cells; this will be followed by transfer of cellular extract into 50ml centrifuge tubes (centrifuged at 20,000 rpm for 17 minutes at 4°C). Thereafter, the supernatant will be aspirated and the pellet will be resuspended in 30ml Membrane Wash Buffer 5 followed by centrifuge at 20,000 rpm for 17 minutes at 4°C. The supernatant will then be aspirated and the pellet resuspended in Binding Buffer. This will then be homogenized using a Brinkman polytron™ homogenizer (15-20 second bursts until the all material is in suspension). This is referred to herein as "Membrane Protein".

2. Bradford Protein Assay

10 Following the homogenization, protein concentration of the membranes will be determined using the Bradford Protein Assay (protein can be diluted to about 1.5mg/ml, aliquoted and frozen (-80°C) for later use; when frozen, protocol for use will be as follows: on the day of the assay, frozen Membrane Protein is thawed at room temperature, followed by vortex and then homogenized with a polytron at about 15 12 x 1,000 rpm for about 5-10 seconds; it was noted that for multiple preparations, the homogenizer should be thoroughly cleaned between homoginezation of different preparations).

a. Materials

Binding Buffer (as per above); Bradford Dye Reagent; Bradford Protein 20 Standard will be utilized, following manufacturer instructions (Biorad, cat. no. 500-0006).

b. Procedure

Duplicate tubes will be prepared, one including the membrane, and one as a control "blank". Each contained 800ul Binding Buffer. Thereafter, 10μl of Bradford 25 Protein Standard (1mg/ml) will be added to each tube, and 10μl of membrane Protein

will then be added to just one tube (not the blank). Thereafter, 200ul of Bradford Dye Reagent will be added to each tube, followed by vortex of each. After five (5) minutes, the tubes will be re-vortexed and the material therein will be transferred to cuvettes. The cuvettes will then be read using a CECIL 3041 spectrophotometer, at 5 wavelength 595.

3. Direct Identification Assay

a. Materials

GDP Buffer consisted of 37.5 ml Binding Buffer and 2mg GDP (Sigma, cat. no. G-7127), followed by a series of dilutions in Binding Buffer to obtain 0.2 μ M GDP 10 (final concentration of GDP in each well was 0.1 μ M GDP); each well comprising a candidate compound, has a final volume of 200ul consisting of 100 μ l GDP Buffer (final concentration, 0.1 μ M GDP), 50 μ l Membrane Protein in Binding Buffer, and 50 μ l [35 S]GTP γ S (0.6 nM) in Binding Buffer (2.5 μ l [35 S]GTP γ S per 10ml Binding Buffer).

b. Procedure

15 Candidate compounds will be preferably screened using a 96-well plate format (these can be frozen at -80°C). Membrane Protein (or membranes with expression vector excluding the GPCR Fusion Protein, as control), will be homogenized briefly until in suspension. Protein concentration will then be determined using the Bradford Protein Assay set forth above. Membrane Protein (and control) will then be diluted to 20 0.25mg/ml in Binding Buffer (final assay concentration, 12.5 μ g/well). Thereafter, 100 μ l GDP Buffer was added to each well of a Wallac ScintistripTM (Wallac). A 5 μ l pin tool will then be used to transfer 5 μ l of a candidate compound into such well (i.e., 5 μ l in total assay volume of 200 μ l is a 1:40 ratio such that the final screening concentration of the candidate compound is 10 μ M). Again, to avoid contamination, after each transfer 25 step the pin tool should be rinsed in three reservoirs comprising water (1X), ethanol (1X)

and water (2X) – excess liquid should be shaken from the tool after each rinse and dried with paper and kimwipes. Thereafter, 50 μ l of Membrane Protein will be added to each well (a control well comprising membranes without the GPCR Fusion Protein was also utilized), and pre-incubated for 5-10 minutes at room temperature. Thereafter, 50 μ l of 5 $[^{35}\text{S}]$ GTP γ S (0.6 nM) in Binding Buffer will be added to each well, followed by incubation on a shaker for 60 minutes at room temperature (again, in this example, plates were covered with foil). The assay will then be stopped by spinning of the plates at 4000 RPM for 15 minutes at 22°C. The plates will then be aspirated with an 8 channel manifold and sealed with plate covers. The plates will then be read on a Wallacc 1450 10 using setting “Prot. #37” (as per manufacturer instructions).

B. Cyclic AMP Assay

Another assay approach to directly identified candidate compound was accomplished by utilizing a cyclase-based assay. In addition to direct identification, this 15 assay approach can be utilized as an independent approach to provide confirmation of the results from the $[^{35}\text{S}]$ GTP γ S approach as set forth above.

A modified Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) was preferably utilized for direct identification of candidate compounds as inverse agonists and agonists to constitutively activated orphan GPCRs in accordance 20 with the following protocol.

Transfected cells were harvested approximately three days after transfection. Membranes were prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM MgCl₂. Homogenization was performed on ice using a Brinkman Polytron™ for approximately 10 seconds. The resulting homogenate is 25 centrifuged at 49,000 X g for 15 minutes at 4°C. The resulting pellet was then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA,

homogenized for 10 seconds, followed by centrifugation at 49,000 X g for 15 minutes at 4°C. The resulting pellet was then stored at -80°C until utilized. On the day of direct identification screening, the membrane pellet was slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM MgCl₂, to yield a 5 final protein concentration of 0.60mg/ml (the resuspended membranes are placed on ice until use).

cAMP standards and Detection Buffer (comprising 2 μ Ci of tracer [¹²⁵I] cAMP (100 μ l) to 11 ml Detection Buffer) were prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer was prepared fresh for screening and 10 contained 20mM HEPES, pH 7.4, 10mM MgCl₂, 20mM phosphocreatine (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 μ M GTP (Sigma), and 0.2 mM ATP (Sigma); Assay Buffer was then stored on ice until utilized.

Candidate compounds identified as per above (if frozen, thawed at room temperature) were added, preferably, to 96-well plate wells (3 μ l/well; 12 μ M final assay 15 concentration), together with 40 μ l Membrane Protein (30 μ g/well) and 50 μ l of Assay Buffer. This admixture was then incubated for 30 minutes at room temperature, with gentle shaking.

Following the incubation, 100 μ l of Detection Buffer was added to each well, followed by incubation for 2-24 hours. Plates were then counted in a Wallac 20 MicroBeta™ plate reader using "Prot. #31" (as per manufacturer instructions).

A representative screening assay plate (96 well format) result is presented in Figure 12. Each bar represents the results for a different compound in each well, plus RUP13-Gsc α Fusion Protein construct, as prepared in Example 5(a) above. The representative results presented in Figure 12 also provide standard deviations based upon 25 the mean results of each plate ("m") and the mean plus two arbitrary preference for

selection of inverse agonists as "leads" from the primary screen involves selection of candidate compounds that reduce the per cent response by at least the mean plate response, minus two standard deviations. Conversely, an arbitrary preference for selection of an agonists as "leads" from the primary screen involves selection of 5 candidate compounds that increase the per cent response by at least the mean plate response, plus the two standard deviations. Based upon these selection processes, the candidate compounds in the following wells were directly identified as putative inverse agonist (Compound A) and agonist (Compound B) to RUP13 in wells A2 and G9, respectively. *See, Figure 12.* It is noted for clarity: these compounds have been directly 10 identified without any knowledge of the endogenous ligand for this GPCR. By focusing on assay techniques that are based upon receptor function, and not compound binding affinity, we are able to ascertain compounds that are able to reduce the functional activity of this receptor (Compound A) as well as increase the functional activity of the receptor (Compound B). Based upon the location of these receptor in lung tissue (see, 15 for example, hRUP13 and hRUP21 in Example 6), pharmaceutical agents can be developed for potential therapeutic treatment of lung cancer.

References cited throughout this patent document, including co-pending and related patent applications, unless otherwise indicated, are fully incorporated herein by reference. Modifications and extension of the disclosed inventions that are within the 20 purview of the skilled artisan are encompassed within the above disclosure and the claims that follow.

Although a variety of expression vectors are available to those in the art, for purposes of utilization for both the endogenous and non-endogenous human GPCRs, it is most preferred that the vector utilized be pCMV. This vector was deposited with the 25 American Type Culture Collection (ATCC) on October 13, 1998 (10801 University

Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

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CLAIMS

What is claimed is:

1. A G protein-coupled receptor encoded by an amino acid sequence of
5 SEQ.ID.NO.:2.
2. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 1.
3. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:1.
4. A host cell comprising the plasmid of claim 3.
- 10 5. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:4.
6. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 5.
7. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:3.
- 15 8. A host cell comprising the plasmid of claim 7.
9. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:6.
10. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 9.
- 20 11. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:5.
12. A host cell comprising the plasmid of claim 11.
13. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:8.
14. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 13.
- 25

15. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:7.
16. A host cell comprising the plasmid of claim 15.
17. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:10.
- 5 18. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 17.
19. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:9.
20. A host cell comprising the plasmid of claim 19.
21. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:12.
- 10 22. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 21 comprising an amino acid sequence of SEQ.ID.NO.84.
23. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:11.
24. A host cell comprising the plasmid of claim 23.
- 15 25. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:14.
26. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 25 comprising an amino acid sequence of SEQ.ID.NO.88.
27. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:13.
- 20 28. A host cell comprising the plasmid of claim 27.
29. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:16.
30. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 29 comprising an amino acid sequence of SEQ.ID.NO.:92.
- 25 31. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:15.

32. A host cell comprising the plasmid of claim 31.
33. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:18.
34. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 33.
- 5 35. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:17.
36. A host cell comprising the plasmid of claim 35.
37. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:20.
- 10 38. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 37.
39. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:19.
40. A host cell comprising the plasmid of claim 39.
41. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:22.
- 15 42. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 41.
43. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:21.
44. A host cell comprising the plasmid of claim 43.
- 20 45. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:24.
46. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 45.
47. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:23.
- 25 48. A host cell comprising the plasmid of claim 47.

49. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:26.
50. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 49.
- 5 51. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:25.
52. A host cell comprising the plasmid of claim 51.
53. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:28.
54. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 53.
- 10 55. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:27.
56. A host cell comprising the plasmid of claim 55.
57. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:30.
- 15 58. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 57.
59. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:29.
60. A host cell comprising the plasmid of claim 59.
61. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:32.
- 20 62. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 61 comprising an amino acid sequence of SEQ.ID.NO.:96.
63. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:95.
64. A host cell comprising the plasmid of claim 63.

65. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:34.
66. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 65.
- 5 67. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:33.
68. A host cell comprising the plasmid of claim 67.
69. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:36.
70. A non-endogenous, constitutively activated version of the G protein-coupled 10 receptor of claim 69.
71. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:35.
72. A host cell comprising the plasmid of claim 71.
73. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:38.
- 15 74. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 73.
75. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:37.
76. A host cell comprising the plasmid of claim 75.
77. A G protein-coupled receptor encoded by an amino acid sequence of 20 SEQ.ID.NO.:40.
78. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 77.
79. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:39.
80. A host cell comprising the plasmid of claim 79.

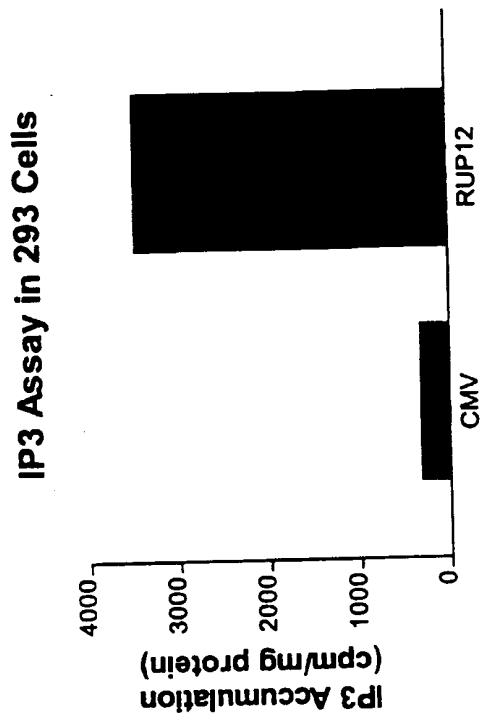


Figure 1

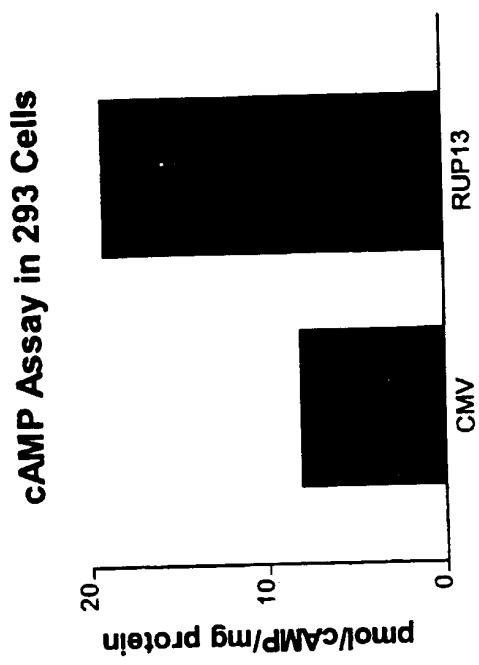


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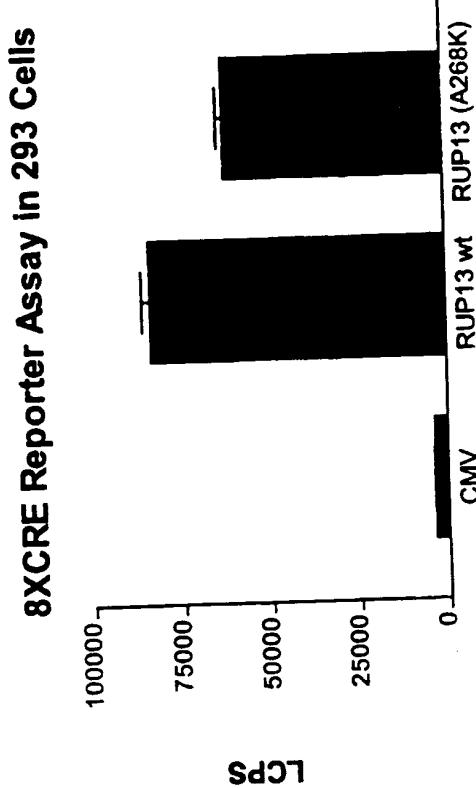


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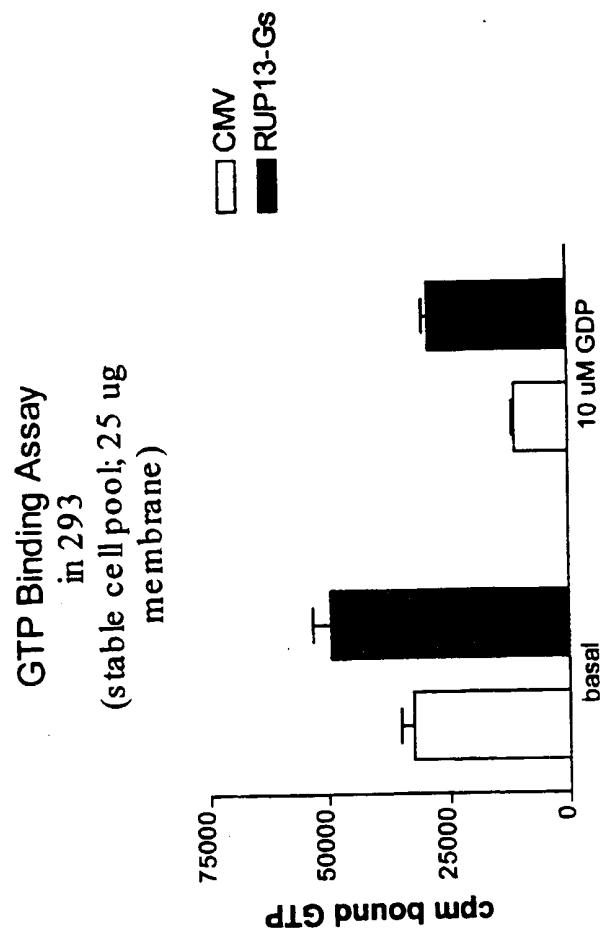


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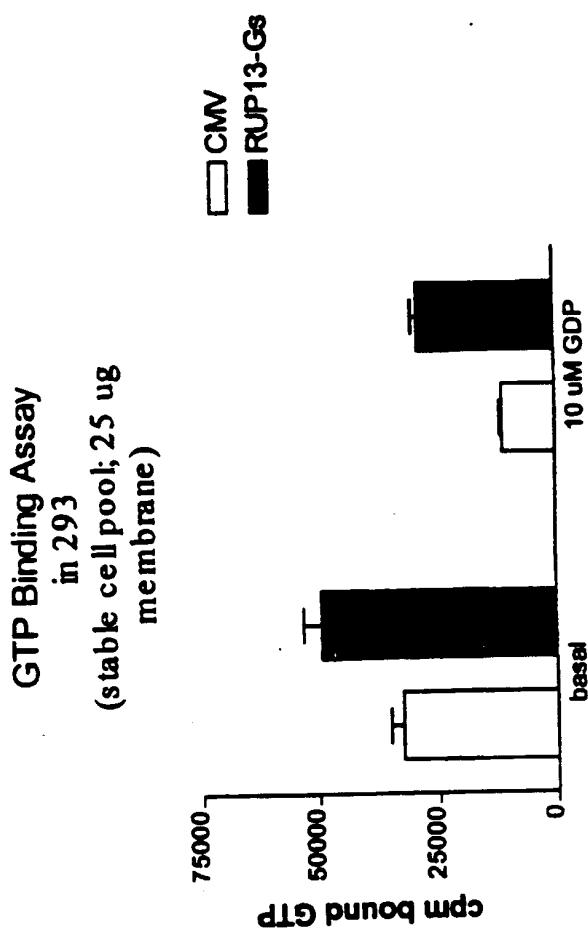


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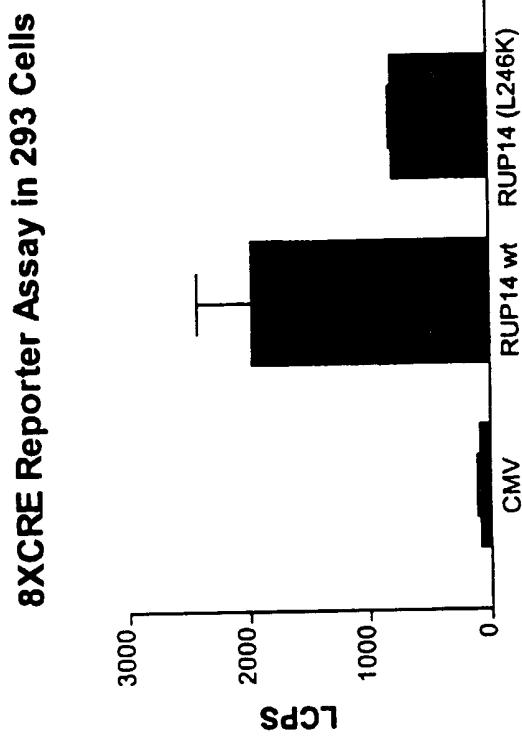


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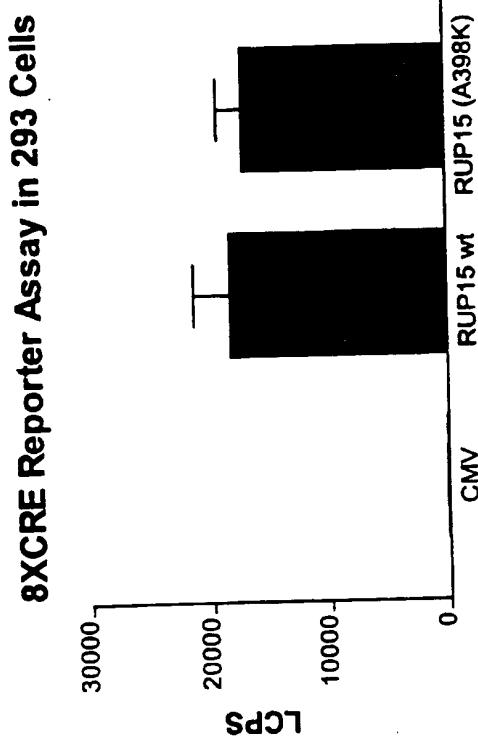


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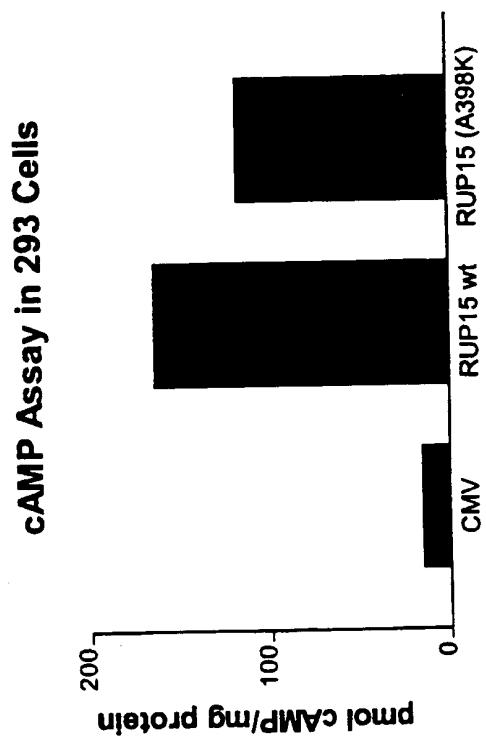


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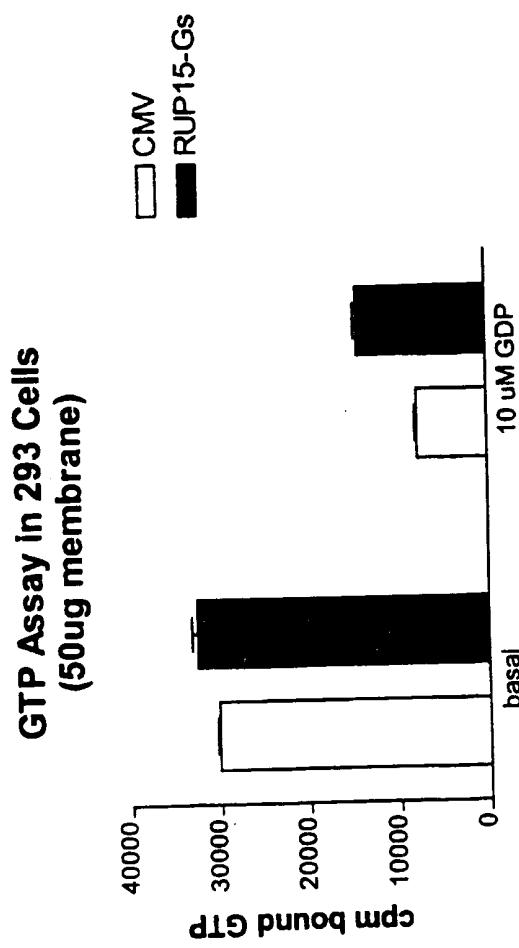


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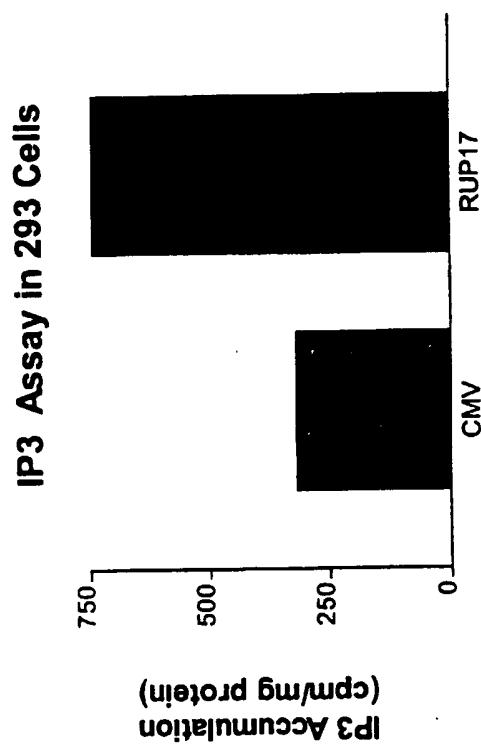


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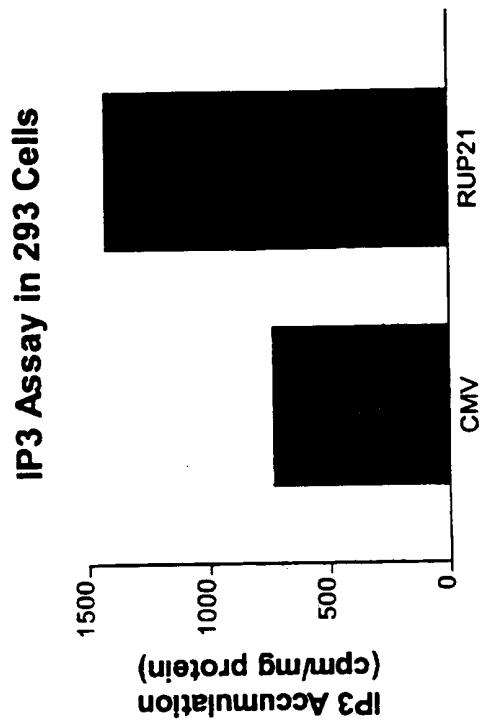


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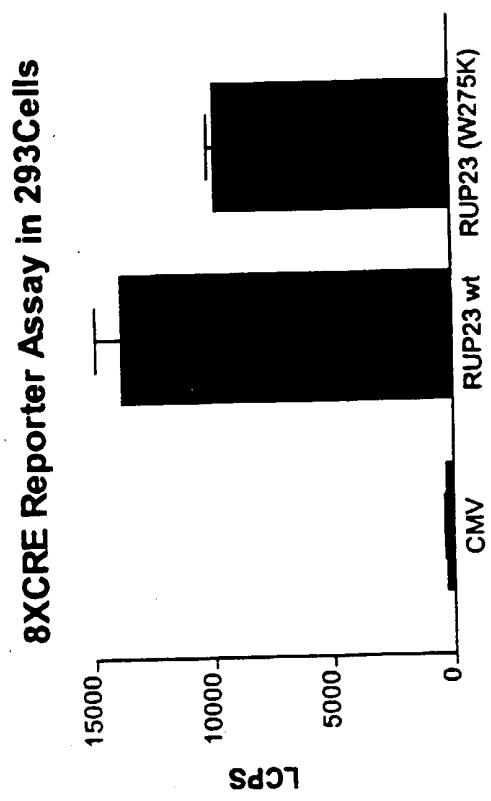


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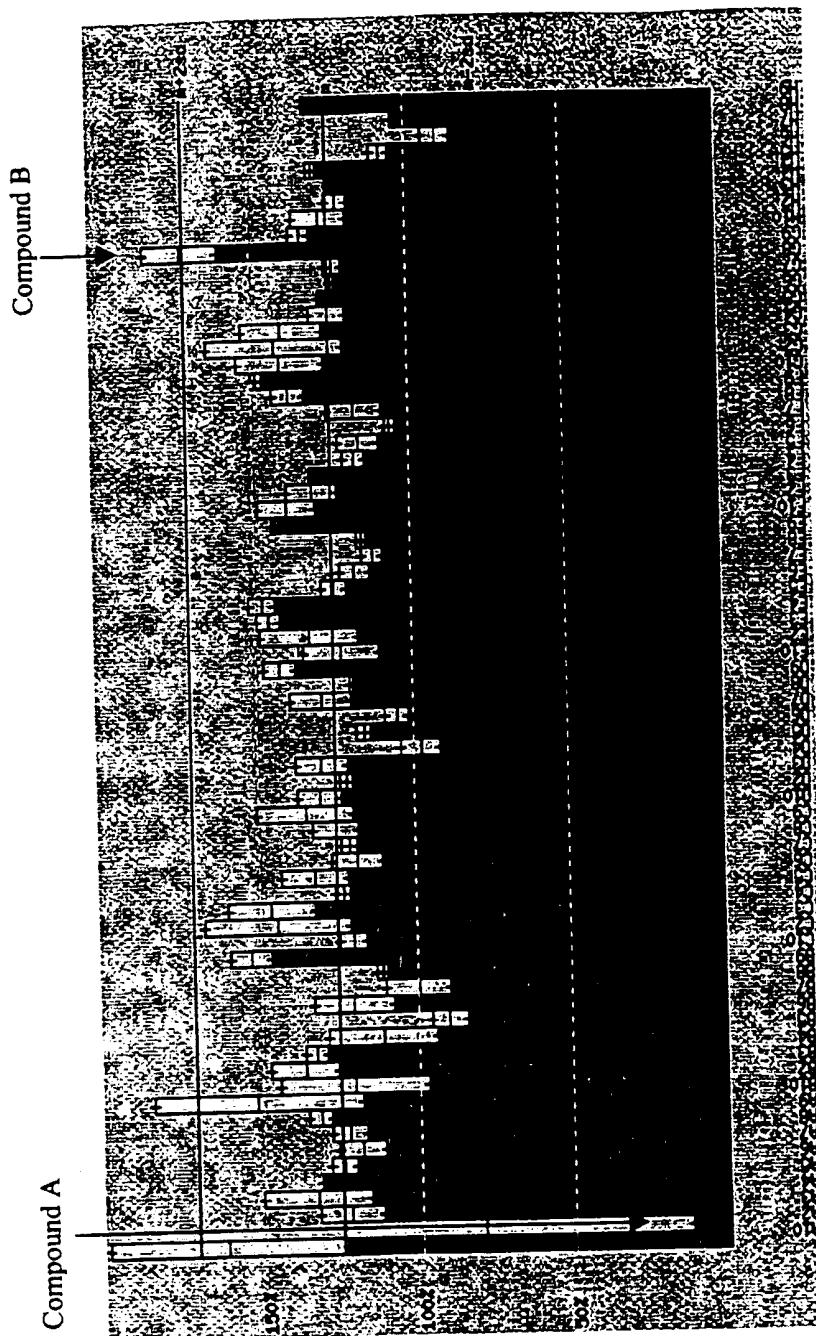


Figure 12

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Dang, Huong T.
Lowitz, Kevin P.

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Phe Phe Ala Ala Lys Ile Val Ile Gly Ile Ala Leu Ala Gly Ile Met
50 55 60
Leu Val Cys Gly Ile Gly Asn Phe Val Phe Ile Ala Ala Leu Thr Arg
65 70 75 80
Tyr Lys Lys Leu Arg Asn Leu Thr Asn Leu Leu Ile Ala Asn Leu Ala
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Ile Ser Asp Phe Leu Val Ala Ile Ile Cys Cys Pro Phe Glu Met Asp
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Val Trp Met Val Ser Ile Leu Ile Ala Ile Pro Ser Ala Tyr Phe Ala
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260 265 270
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 Arg Arg Arg Val Gly Ala Thr Trp Leu Leu His Leu Ala Val Ala Asp
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 Gly Gly His Trp Pro Tyr Gly Ala Val Gly Cys Arg Ala Leu Pro Ser
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 Ile Ile Leu Leu Thr Met Tyr Ala Ser Val Leu Leu Leu Ala Ala Leu
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Gly Pro Cys His Pro Thr Ser Ser Leu Val Ser Ala Phe Leu Ala			
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Gly Ala Ala Ala Cys Lys Val Asn Leu Phe Met Leu Ser Thr Asn Arg			
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Thr Ala Ser Val Val Phe Leu Thr Ala Ile Ala Leu Asn Arg Tyr Leu			
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Arg Val Gly Thr Lys Pro Ser Ala Ser Leu Arg Trp His Gln Ala Leu			
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Tyr Leu Leu Glu Phe Phe Leu Pro Leu Ala Leu Ile Leu Phe Ala Ile			
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275	280	285	
Gly Pro Gln Arg Ala Met Arg Val Leu Ala Met Val Val Ala Val Tyr			
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Thr Ile Cys Phe Leu Pro Ser Ile Ile Phe Gly Met Ala Ser Met Val			
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Ala Phe Trp Leu Ser Ala Cys Arg Ser Leu Asp Leu Cys Thr Gln Leu			
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Phe His Gly Ser Leu Ala Phe Thr Tyr Leu Asn Ser Val Leu Asp Pro			
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Val Leu Tyr Cys Phe Ser Ser Pro Asn Phe Leu His Gln Ser Arg Ala			
355	360	365	

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 tcacgcctct cctcgccgt aagcagcagc gccaaccccg tcatctactt cctggtgggc 840
 agccggagga gcccacaggct gcccaccagg tccctgggaa ctgtgctcca acaggcgctt 900
 cgcgaggagc ccgagctgga aggtggggag acgcccaccg tggcaccaa tgagatgggg 960
 966
 gcttga

<210> 10

<211> 321

<212> PRT

<213> Homo sapiens

<400> 10

Met Asn Gln Thr Leu Asn Ser Ser Gly Thr Val Glu Ser Ala Leu Asn
 1 5 10 15

Tyr Ser Arg Gly Ser Thr Val His Thr Ala Tyr Leu Val Leu Ser Ser
 20 25 30

Leu Ala Met Phe Thr Cys Leu Cys Gly Met Ala Gly Asn Ser Met Val
 35 40 45
 Ile Trp Leu Leu Gly Phe Arg Met His Arg Asn Pro Phe Cys Ile Tyr
 50 55 60
 Ile Leu Asn Leu Ala Ala Ala Asp Leu Leu Phe Leu Phe Ser Met Ala
 65 70 75 80
 Ser Thr Leu Ser Leu Glu Thr Gln Pro Leu Val Asn Thr Thr Asp Lys
 85 90 95
 Val His Glu Leu Met Lys Arg Leu Met Tyr Phe Ala Tyr Thr Val Gly
 100 105 110
 Leu Ser Leu Leu Thr Ala Ile Ser Thr Gln Arg Cys Leu Ser Val Leu
 115 120 125
 Phe Pro Ile Trp Phe Lys Cys His Arg Pro Arg His Leu Ser Ala Trp
 130 135 140
 Val Cys Gly Leu Leu Trp Thr Leu Cys Leu Leu Met Asn Gly Leu Thr
 145 150 155 160
 Ser Ser Phe Cys Ser Lys Phe Leu Lys Phe Asn Glu Asp Arg Cys Phe
 165 170 175
 Arg Val Asp Met Val Gln Ala Ala Leu Ile Met Gly Val Leu Thr Pro
 180 185 190
 Val Met Thr Leu Ser Ser Leu Thr Leu Phe Val Trp Val Arg Arg Ser
 195 200 205
 Ser Gln Gln Trp Arg Arg Gln Pro Thr Arg Leu Phe Val Val Val Leu
 210 215 220
 Ala Ser Val Leu Val Phe Leu Ile Cys Ser Leu Pro Leu Ser Ile Tyr
 225 230 235 240
 Trp Phe Val Leu Tyr Trp Leu Ser Leu Pro Pro Glu Met Gln Val Leu
 245 250 255
 Cys Phe Ser Leu Ser Arg Leu Ser Ser Val Ser Ser Ala Asn
 260 265 270
 Pro Val Ile Tyr Phe Leu Val Gly Ser Arg Arg Ser His Arg Leu Pro
 275 280 285
 Thr Arg Ser Leu Gly Thr Val Leu Gln Gln Ala Leu Arg Glu Glu Pro
 290 295 300
 Glu Leu Glu Gly Gly Glu Thr Pro Thr Val Gly Thr Asn Glu Met Gly
 305 310 315 320

Ala

<210> 11
 <211> 1356
 <212> DNA
 <213> Homo sapiens

<400> 11
 atggagtccct caccatcccc ccagtcatca ggaaactctt ccactttggg gagggtcctt 60

caaaccagg	gtccctctac	tgccagtgg	gtcccgagg	tggggctacg	ggatgttgc	120
tcggaaatcg	tggcccttct	cttcatgtc	ctgctggact	tgactgtgt	ggctggcaat	180
gccgctgtga	tggccgtgat	cgcgaagacg	cctgcccctcc	gaaaatttgt	cttcgtcttc	240
cacctctgcc	tggtggacct	gctggctgcc	ctgaccctca	tgcccctggc	catgtctcc	300
agctctgccc	tcttgacca	cgcgcctttt	ggggaggtgg	cctgcccctt	ctacttgttt	360
ctgagcgtgt	gttttgcag	cctggccatc	ctctcggtgt	cagccatcaa	tgtggagcgc	420
tactattacg	tagtccaccc	catgcgtac	gaggtgcgc	tgacgctggg	gctggtgccc	480
tctgtgctgg	tgggtgtgt	ggtgaaggcc	ttggccatgg	cttctgtgcc	agtgttggga	540
agggtctcct	gggaggaagg	agctccca	gtccccccag	gctgttca	ccagtggagc	600
cacagtgcct	actgcccac	ttttgtgg	gtctttgt	tcctttactt	tctgttgc	660
ctgctcctca	tacttgtgt	ctactgcagc	atgttccag	tggcccgct	ggctgccc	720
cagcacgggc	cgctgcccac	gtggatggag	acacccggc	aacgctccga	atctctcagc	780
agccgtcaca	cgatggtcac	cagctcgggg	gccccccaga	ccacccacaca	ccggacgttt	840
gggggaggg	aagcagca	ggttctcctg	gctgtgggg	gacagttcct	gctctgttgg	900
ttgcccact	tctcttcca	cctctatgtt	gccctgagtg	ctcagccat	ttcaactgg	960
caggtggaga	gtgtggtcac	ctggattggc	tactttgt	tcacttccaa	ccctttcttc	1020
tatggatgtc	tcaaccggca	gatccgggg	gagctcagca	agcagttgt	ctgcttcttc	1080
aagccagtc	cagaggagga	gctgaggctg	cctagccgg	agggctccat	tgaggagaac	1140
ttcctgcagt	tccttcaggg	gactggctgt	ccttctgagt	cctgggtt	ccgaccctta	1200
cccagccca	agcaggagcc	acctgctgtt	gactttcgaa	tcccaggcca	gatagctgag	1260
gagacctctg	agttcctgga	gcagcaactc	accagcgaca	tcatcatgtc	agacagctac	1320
ctccgtcc	ccgcctcacc	ccggctggag	tcatga			1356

<210> 12
 <211> 451
 <212> PRT
 <213> Homo sapiens

<400> 12

Met Glu Ser Ser Pro Ile Pro Gln Ser Ser Gly Asn Ser Ser Thr Leu
 1 5 10 15

Gly Arg Val Pro Gln Thr Pro Gly Pro Ser Thr Ala Ser Gly Val Pro
 20 25 30

Glu Val Gly Leu Arg Asp Val Ala Ser Glu Ser Val Ala Leu Phe Phe
 35 40 45

Met Leu Leu Leu Asp Leu Thr Ala Val Ala Gly Asn Ala Ala Val Met
 50 55 60

Ala Val Ile Ala Lys Thr Pro Ala Leu Arg Lys Phe Val Phe Val Phe
 65 70 75 80
 His Leu Cys Leu Val Asp Leu Leu Ala Ala Leu Thr Leu Met Pro Leu
 85 90 95
 Ala Met Leu Ser Ser Ser Ala Leu Phe Asp His Ala Leu Phe Gly Glu
 100 105 110
 Val Ala Cys Arg Leu Tyr Leu Phe Leu Ser Val Cys Phe Val Ser Leu
 115 120 125
 Ala Ile Leu Ser Val Ser Ala Ile Asn Val Glu Arg Tyr Tyr Tyr Val
 130 135 140
 Val His Pro Met Arg Tyr Glu Val Arg Met Thr Leu Gly Leu Val Ala
 145 150 155 160
 Ser Val Leu Val Gly Val Trp Val Lys Ala Leu Ala Met Ala Ser Val
 165 170 175
 Pro Val Leu Gly Arg Val Ser Trp Glu Glu Gly Ala Pro Ser Val Pro
 180 185 190
 Pro Gly Cys Ser Leu Gln Trp Ser His Ser Ala Tyr Cys Gln Leu Phe
 195 200 205
 Val Val Val Phe Ala Val Leu Tyr Phe Leu Leu Pro Leu Leu Ile
 210 215 220
 Leu Val Val Tyr Cys Ser Met Phe Arg Val Ala Arg Val Ala Ala Met
 225 230 235 240
 Gln His Gly Pro Leu Pro Thr Trp Met Glu Thr Pro Arg Gln Arg Ser
 245 250 255
 Glu Ser Leu Ser Ser Arg Ser Thr Met Val Thr Ser Ser Gly Ala Pro
 260 265 270
 Gln Thr Thr Pro His Arg Thr Phe Gly Gly Lys Ala Ala Val Val
 275 280 285
 Leu Leu Ala Val Gly Gly Gln Phe Leu Leu Cys Trp Leu Pro Tyr Phe
 290 295 300
 Ser Phe His Leu Tyr Val Ala Leu Ser Ala Gln Pro Ile Ser Thr Gly
 305 310 315 320
 Gln Val Glu Ser Val Val Thr Trp Ile Gly Tyr Phe Cys Phe Thr Ser
 325 330 335
 Asn Pro Phe Phe Tyr Gly Cys Leu Asn Arg Gln Ile Arg Gly Glu Leu
 340 345 350
 Ser Lys Gln Phe Val Cys Phe Phe Lys Pro Ala Pro Glu Glu Glu Leu
 355 360 365
 Arg Leu Pro Ser Arg Glu Gly Ser Ile Glu Glu Asn Phe Leu Gln Phe
 370 375 380
 Leu Gln Gly Thr Gly Cys Pro Ser Glu Ser Trp Val Ser Arg Pro Leu
 385 390 395 400
 Pro Ser Pro Lys Gln Glu Pro Pro Ala Val Asp Phe Arg Ile Pro Gly
 405 410 415

Gln Ile Ala Glu Glu Thr Ser Glu Phe Leu Glu Gln Gln Leu Thr Ser
 420 425 430

Asp Ile Ile Met Ser Asp Ser Tyr Leu Arg Pro Ala Ala Ser Pro Arg
 435 440 445

Leu Glu Ser
 450

<210> 13
 <211> 1041
 <212> DNA
 <213> Homo sapiens

<400> 13
 atggagagaa aatttatgtc cttgcaacca tccatctccg tatcagaaaat ggaaccaaat 60
 ggcaccttca gcaataacaa cagcaggaac tgccacaattt aaaaacttcaa gagagaattt 120
 ttcccaattt tatatatgtat aatatttttc tggggagttct tggggaaatgg gttgtccata 180
 tatgttttcc tgcagcctta taagaagtcc acatctgtga acgttttcat gctaaatctg 240
 gccatttcag atctcctgtt cataaggcacc cttcccttca gggctgacta ttatctttaga 300
 ggctccaattt ggatattttgg agacctggcc tgcaggattt tgcattttttt cttgtatgtc 360
 aacatgtaca gcagtattta tttccctgacc gtgcgttgc ttgtgcgttt cctggcaatg 420
 gttcaccctt ttcggcttct gcatgtcacc agcatcagga gtgcctggat cctctgtggg 480
 atcatatggc tccttatcat ggcttcctca ataatgtcc tggacagtgg ctctgagcag 540
 aacggcagtgc tcacatcatg cttagagctg aatctctata aaattgtctaa gtcgcagacc 600
 atgaactata ttgccttggg ggtgggctgc ctgcgtccat tttcacactt cagcatctgt 660
 tatctgtca tcattcgggt tctgttaaaa gtggagggtcc cagaatcggg gtcgcgggtt 720
 tctcacagga aggcactgac caccatcatc atcaccttgc tcattttttt cttgttgc 780
 ctgccttac acacactgag gaccgtccac ttgcgtccat ggaaagtggg tttatgc 840
 gacagactgc ataaagcttt ggttatcaca ctggccttgg cagcagccaa tgccgttcc 900
 aatcctctgc tcttactt tgctggggag aattttaagg acagactaaa gtctgcactc 960
 agaaaaggcc atccacagaa ggcaaagaca aagtgtgtt tccctgttag tgcgtgggtt 1020
 agaaaggaaa caagagtata a 1041

<210> 14
 <211> 346
 <212> PRT
 <213> Homo sapiens

<400> 14

Met Glu Arg Lys Phe Met Ser Leu Gln Pro Ser Ile Ser Val Ser Glu
 1 5 10 15

Met Glu Pro Asn Gly Thr Phe Ser Asn Asn Asn Ser Arg Asn Cys Thr
 20 25 30

Ile Glu Asn Phe Lys Arg Glu Phe Phe Pro Ile Val Tyr Leu Ile Ile
 35 40 45
 Phe Phe Trp Gly Val Leu Gly Asn Gly Leu Ser Ile Tyr Val Phe Leu
 50 55 60
 Gln Pro Tyr Lys Lys Ser Thr Ser Val Asn Val Phe Met Leu Asn Leu
 65 70 75 80
 Ala Ile Ser Asp Leu Leu Phe Ile Ser Thr Leu Pro Phe Arg Ala Asp
 85 90 95
 Tyr Tyr Leu Arg Gly Ser Asn Trp Ile Phe Gly Asp Leu Ala Cys Arg
 100 105 110
 Ile Met Ser Tyr Ser Leu Tyr Val Asn Met Tyr Ser Ser Ile Tyr Phe
 115 120 125
 Leu Thr Val Leu Ser Val Val Arg Phe Leu Ala Met Val His Pro Phe
 130 135 140
 Arg Leu Leu His Val Thr Ser Ile Arg Ser Ala Trp Ile Leu Cys Gly
 145 150 155 160
 Ile Ile Trp Ile Leu Ile Met Ala Ser Ser Ile Met Leu Leu Asp Ser
 165 170 175
 Gly Ser Glu Gln Asn Gly Ser Val Thr Ser Cys Leu Glu Leu Asn Leu
 180 185 190
 Tyr Lys Ile Ala Lys Leu Gln Thr Met Asn Tyr Ile Ala Leu Val Val
 195 200 205
 Gly Cys Leu Leu Pro Phe Phe Thr Leu Ser Ile Cys Tyr Leu Leu Ile
 210 215 220
 Ile Arg Val Leu Leu Lys Val Glu Val Pro Glu Ser Gly Leu Arg Val
 225 230 235 240
 Ser His Arg Lys Ala Leu Thr Thr Ile Ile Thr Leu Ile Ile Phe
 245 250 255
 Phe Leu Cys Phe Leu Pro Tyr His Thr Leu Arg Thr Val His Leu Thr
 260 265 270
 Thr Trp Lys Val Gly Leu Cys Lys Asp Arg Leu His Lys Ala Leu Val
 275 280 285
 Ile Thr Leu Ala Leu Ala Ala Asn Ala Cys Phe Asn Pro Leu Leu
 290 295 300
 Tyr Tyr Phe Ala Gly Glu Asn Phe Lys Asp Arg Leu Lys Ser Ala Leu
 305 310 315 320
 Arg Lys Gly His Pro Gln Lys Ala Lys Thr Lys Cys Val Phe Pro Val
 325 330 335
 Ser Val Trp Leu Arg Lys Glu Thr Arg Val
 340 345
 <210> 15
 <211> 1527
 <212> DNA
 <213> Homo sapiens

<400> 15
 atgacgtcca cctgcaccaa cagcacgcgc gagagtaaca gcagccacac gtgcacgtccc 60
 ctctccaaaa tgcccatcag cctggccac ggcacatcatcc gctcaaccgt gctggttatac 120
 ttcctcgccg cctcttcgt cggcaacata gtgctggcgc tagtgttgca gcgcaagccg 180
 cagctgctgc aggtgaccaa ccgttttatac ttaaacctcc tcgtcaccga cctgctgcag 240
 atttcgctcg tggccccctg ggtggggcc acctctgtgc ctctcttctg gcccctcaac 300
 agccacttct gcacggccct ggttagcctc acccacctgt tcgccttcgc cagcgtcaac 360
 accattgtcg tgggtcagt ggatcgctac ttgtccatca tccaccctct ctcctaccccg 420
 tccaagatga cccagcgcgg cggttacctg ctccctatgt gcacctggat tggccatc 480
 ctgcagagca ctccctccact ctacggctgg ggccaggctg cctttgatga gcgcaatgct 540
 ctctgctcca tggatctgggg ggccagcccc agctacacta ttctcagcgt ggtgtccctc 600
 atcgtcattc cactgattgt catgattgcc tgctactccg tgggtttctg tgcagccgg 660
 aggccatcg ctctgctgtaa caatgtcaag agacacagct tggaagtgcg agtcaaggac 720
 tgggtggaga atgaggatga agagggagca gagaagaagg aggagttcca ggatgagagt 780
 gagtttcgccc gccagcatga aggtgaggc aaggccaagg agggcagaat ggaagccaag 840
 gacggcagcc tgaaggccaa ggaaggaagc acggggacca gtgagagtag tggtagaggcc 900
 aggggcagcg aggaggtcag agagagcgc acgggtggcca ggcacggcag catggagggt 960
 aaggaaggca gcaccaaagt tgaggagaac agcatgaagg cagacaaggg tcgcacagag 1020
 gtcaaccagt gcagcattga ctgggtgaa gatgacatgg agttggatga agacgacatc 1080
 aatttcagtg aggtgacgt cgaggcagtgc aacatcccg agagcctccc acccagtcgt 1140
 ctgtaaacagca acagcaaccc tcctctgccc aggtgctacc agtgcaaaagc tgctaaagt 1200
 atcttcatca tcattttctc ctatgtgcta tccctggggc cctactgctt tttagcagtc 1260
 ctggccgtgt ggggtggatgt cgaaacccag gtaccccaagt ggggtgatcac cataatcatc 1320
 tggctttct tcctgcagtg ctgcacccac ccctatgtct atggctacat gcacaagacc 1380
 attaagaagg aaatccagga catgctgaag aagttttctc gcaaggaaaa gccccggaaa 1440
 gaagatagcc acccagaccc gcccggaaaca gagggtggga ctgaaggcaa gattgtccct 1500
 tcctacgatt ctgctacttt tccttga 1527

<210> 16
 <211> 508
 <212> PRT
 <213> Homo sapiens
 <400> 16

Met Thr Ser Thr Cys Thr Asn Ser Thr Arg Glu Ser Asn Ser Ser His
 1 5 10 15

Thr Cys Met Pro Leu Ser Lys Met Pro Ile Ser Leu Ala His Gly Ile
 20 25 30
 Ile Arg Ser Thr Val Leu Val Ile Phe Leu Ala Ala Ser Phe Val Gly
 35 40 45
 Asn Ile Val Leu Ala Leu Val Leu Gln Arg Lys Pro Gln Leu Leu Gln
 50 55 60
 Val Thr Asn Arg Phe Ile Phe Asn Leu Leu Val Thr Asp Leu Leu Gln
 65 70 75 80
 Ile Ser Leu Val Ala Pro Trp Val Val Ala Thr Ser Val Pro Leu Phe
 85 90 95
 Trp Pro Leu Asn Ser His Phe Cys Thr Ala Leu Val Ser Leu Thr His
 100 105 110
 Leu Phe Ala Phe Ala Ser Val Asn Thr Ile Val Val Val Ser Val Asp
 115 120 125
 Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr
 130 135 140
 Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile
 145 150 155 160
 Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp
 165 170 175
 Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr
 180 185 190
 Thr Ile Leu Ser Val Val Ser Phe Ile Val Ile Pro Leu Ile Val Met
 195 200 205
 Ile Ala Cys Tyr Ser Val Val Phe Cys Ala Ala Arg Arg Gln His Ala
 210 215 220
 Leu Leu Tyr Asn Val Lys Arg His Ser Leu Glu Val Arg Val Lys Asp
 225 230 235 240
 Cys Val Glu Asn Glu Asp Glu Glu Gly Ala Glu Lys Lys Glu Glu Phe
 245 250 255
 Gln Asp Glu Ser Glu Phe Arg Arg Gln His Glu Gly Glu Val Lys Ala
 260 265 270
 Lys Glu Gly Arg Met Glu Ala Lys Asp Gly Ser Leu Lys Ala Lys Glu
 275 280 285
 Gly Ser Thr Gly Thr Ser Glu Ser Ser Val Glu Ala Arg Gly Ser Glu
 290 295 300
 Glu Val Arg Glu Ser Ser Thr Val Ala Ser Asp Gly Ser Met Glu Gly
 305 310 315 320
 Lys Glu Gly Ser Thr Lys Val Glu Glu Asn Ser Met Lys Ala Asp Lys
 325 330 335
 Gly Arg Thr Glu Val Asn Gln Cys Ser Ile Asp Leu Gly Glu Asp Asp
 340 345 350
 Met Glu Phe Gly Glu Asp Asp Ile Asn Phe Ser Glu Asp Asp Val Glu
 355 360 365

Ala Val Asn Ile Pro Glu Ser Leu Pro Pro Ser Arg Arg Asn Ser Asn
 370 375 380
 Ser Asn Pro Pro Leu Pro Arg Cys Tyr Gln Cys Lys Ala Ala Lys Val
 385 390 395 400
 Ile Phe Ile Ile Ile Phe Ser Tyr Val Leu Ser Leu Gly Pro Tyr Cys
 405 410 415
 Phe Leu Ala Val Leu Ala Val Trp Val Asp Val Glu Thr Gln Val Pro
 420 425 430
 Gln Trp Val Ile Thr Ile Ile Trp Leu Phe Phe Leu Gln Cys Cys
 435 440 445
 Ile His Pro Tyr Val Tyr Gly Tyr Met His Lys Thr Ile Lys Lys Glu
 450 455 460
 Ile Gln Asp Met Leu Lys Lys Phe Phe Cys Lys Glu Lys Pro Pro Lys
 465 470 475 480
 Glu Asp Ser His Pro Asp Leu Pro Gly Thr Glu Gly Gly Thr Glu Gly
 485 490 495
 Lys Ile Val Pro Ser Tyr Asp Ser Ala Thr Phe Pro
 500 505

<210> 17
 <211> 1068
 <212> DNA
 <213> Homo sapiens

<400> 17
 atgcccgtga cggacggcat ttcttcattt gaggacctct tggctaaacaa tatccctcaga 60
 atatttgtct gggttatagc tttcattacc tgctttggaa atcttttgtt cattggcatg 120
 agatctttca ttaaagctga aaatacaact cacgctatgt ccatcaaaat cctttgtgc 180
 gctgattgcc tcatgggtgt ttacttggtc tttgttggca tttcgatataaaaatccga 240
 gggcagttatc agaagtatgc cttgctgtgg atggagagcg tgcagtgccg cctcatgggg 300
 ttccctggca tgctgtccac cgaagtctct gttctgtac tgacctactt gactttggag 360
 aagttccctgg tcattgtctt ccccttcagt aacattcgac ctggaaaacg gcagacctca 420
 gtcatcctca tttgcatttg gatggcgaaa ttttaatag ctgtaattcc attttggaaat 480
 aaggattttt ttggaaactt ttatggaaa aatggagtat gtttccact ttattatgac 540
 caaacagaag atatttggaaag caaagggtat tctcttggaa ttttcctagg tgtgaacttg 600
 ctggcttttc tcatcattgt gtttcctat attactatgt tctgttccat tcaaaaaacc 660
 gccttgcaga ccacagaagt aaggaattgt tttgaaagag aggtggctgt tgcaaatcg 720
 ttctttttta tagtgttctc tgatgccatc tgctggattc ctgtatttgt agttaaaatc 780
 cttccctct tccgggtgga aataccagac acaatgactt cctggatagt gattttttc 840
 cttccagttt acagtgtttt gaatccaatc ctctatactc tcacaaccaa ctttttaag 900
 gacaagttga aacagctgct gcacaaacat cagaggaaat caatttcaa aataaaaaaaaa 960

aaaagtttat ctacatccat tgtgtggata gaggactct cttccctgaa acttggggtt 1020
ttgaacaaaa taacacttgg agacagtata atgaaaccag tttcctag 1068

<210> 18
<211> 355
<212> PRT
<213> Homo sapiens

<400> 18

Met Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu Leu Ala Asn
1 5 10 15
Asn Ile Leu Arg Ile Phe Val Trp Val Ile Ala Phe Ile Thr Cys Phe
20 25 30
Gly Asn Leu Phe Val Ile Gly Met Arg Ser Phe Ile Lys Ala Glu Asn
35 40 45
Thr Thr His Ala Met Ser Ile Lys Ile Leu Cys Cys Ala Asp Cys Leu
50 55 60
Met Gly Val Tyr Leu Phe Phe Val Gly Ile Phe Asp Ile Lys Tyr Arg
65 70 75 80
Gly Gln Tyr Gln Lys Tyr Ala Leu Leu Trp Met Glu Ser Val Gln Cys
85 90 95
Arg Leu Met Gly Phe Leu Ala Met Leu Ser Thr Glu Val Ser Val Leu
100 105 110
Leu Leu Thr Tyr Leu Thr Leu Glu Lys Phe Leu Val Ile Val Phe Pro
115 120 125
Phe Ser Asn Ile Arg Pro Gly Lys Arg Gln Thr Ser Val Ile Leu Ile
130 135 140
Cys Ile Trp Met Ala Gly Phe Leu Ile Ala Val Ile Pro Phe Trp Asn
145 150 155 160
Lys Asp Tyr Phe Gly Asn Phe Tyr Gly Lys Asn Gly Val Cys Phe Pro
165 170 175
Leu Tyr Tyr Asp Gln Thr Glu Asp Ile Gly Ser Lys Gly Tyr Ser Leu
180 185 190
Gly Ile Phe Leu Gly Val Asn Leu Leu Ala Phe Leu Ile Ile Val Phe
195 200 205
Ser Tyr Ile Thr Met Phe Cys Ser Ile Gln Lys Thr Ala Leu Gln Thr
210 215 220
Thr Glu Val Arg Asn Cys Phe Gly Arg Glu Val Ala Val Ala Asn Arg
225 230 235 240
Phe Phe Phe Ile Val Phe Ser Asp Ala Ile Cys Trp Ile Pro Val Phe
245 250 255
Val Val Lys Ile Leu Ser Leu Phe Arg Val Glu Ile Pro Asp Thr Met
260 265 270
Thr Ser Trp Ile Val Ile Phe Phe Leu Pro Val Asn Ser Ala Leu Asn

275 280 285
Pro Ile Leu Tyr Thr Leu Thr Thr Asn Phe Phe Lys Asp Lys Leu Lys
290 295 300
Gln Leu Leu His Lys His Gln Arg Lys Ser Ile Phe Lys Ile Lys Lys
305 310 315 320
Lys Ser Leu Ser Thr Ser Ile Val Trp Ile Glu Asp Ser Ser Ser Leu
325 330 335
Lys Leu Gly Val Leu Asn Lys Ile Thr Leu Gly Asp Ser Ile Met Lys
340 345 350

Pro Val Ser
355

<210> 19
<211> 969
<212> DNA
<213> Homo sapiens

<400> 19
atggatccaa ccatctcaac cttggacaca gaactgacac caatcaacgg aactgaggag 60
actctttgct acaaggcagac cttgaggcctc acgggtgctga cgtgcacatgt ttcccttgtc 120
gggctgacag gaaacgcagt tgtgtctgg ctccctggct gccgcacatgc caggaacgcc 180
ttctccatct acatcctcaa cttggccgca gcagacttcc tcttcctcag cggccgcctt 240
atataattccc tgttaagctt catcagtatc ccccatatcca tctctaaaat cctctatcct 300
gtgatgtatgt tttccctactt tgcaggcctg agctttctga gtgccgtgag caccgagcgc 360
tgcctgtccg tcctgtggcc catctggta cgcgtccacc gccccacaca cctgtcagcg 420
gtgggtgtg tcctgctctg ggcctgtcc ctgctgcgga gcatcctgga gtggatgtta 480
tgtggcttcc tgttcagtgg tgctgattct gcttgggtgtc aaacatcaga tttcatcaca 540
gtcgcgtggc tgatttttt atgtgtggtt ctctgtgggt ccagcctgggt cctgctgatc 600
aggattctct gtggatcccg gaagataccg ctgaccaggc tgtacgtgac catcctgctc 660
acagtaactgg tcttcctccct ctgtggcctg cccttggca ttcagttttt cctatttta 720
tggatccacg tggacaggga agtcttattt tgtcatgttc atctagtttc tattttcctg 780
tccgctctta acagcagtgc caaccccatc atttacttct tcgtgggctc cttaggcag 840
cgtcaaaata ggcagaacct gaagctgggtt ctccagaggg ctctgcagga cgcgtctgag 900
gtggatgaag gtggagggca gcttcctgag gaaatcctgg agctgtcggg aagcagattg 960
gagcagtga 969

<210> 20
<211> 322
<212> PRT
<213> Homo sapiens

<400> 20

Met Asp Pro Thr Ile Ser Thr Leu Asp Thr Glu Leu Thr Pro Ile Asn
1 5 10 15

Gly Thr Glu Glu Thr Leu Cys Tyr Lys Gln Thr Leu Ser Leu Thr Val
20 25 30

Leu Thr Cys Ile Val Ser Leu Val Gly Leu Thr Gly Asn Ala Val Val
35 40 45

Leu Trp Leu Leu Gly Cys Arg Met Arg Arg Asn Ala Phe Ser Ile Tyr
50 55 60

Ile Leu Asn Leu Ala Ala Asp Phe Leu Phe Leu Ser Gly Arg Leu
65 70 75 80

Ile Tyr Ser Leu Leu Ser Phe Ile Ser Ile Pro His Thr Ile Ser Lys
85 90 95

Ile Leu Tyr Pro Val Met Phe Ser Tyr Phe Ala Gly Leu Ser Phe
100 105 110

Leu Ser Ala Val Ser Thr Glu Arg Cys Leu Ser Val Leu Trp Pro Ile
115 120 125

Trp Tyr Arg Cys His Arg Pro Thr His Leu Ser Ala Val Val Cys Val
130 135 140

Leu Leu Trp Ala Leu Ser Leu Leu Arg Ser Ile Leu Glu Trp Met Leu
145 150 155 160

Cys Gly Phe Leu Phe Ser Gly Ala Asp Ser Ala Trp Cys Gln Thr Ser
165 170 175

Asp Phe Ile Thr Val Ala Trp Leu Ile Phe Leu Cys Val Val Leu Cys
180 185 190

Gly Ser Ser Leu Val Leu Leu Ile Arg Ile Leu Cys Gly Ser Arg Lys
195 200 205

Ile Pro Leu Thr Arg Leu Tyr Val Thr Ile Leu Leu Thr Val Leu Val
210 215 220

Phe Leu Leu Cys Gly Leu Pro Phe Gly Ile Gln Phe Phe Leu Phe Leu
225 230 235 240

Trp Ile His Val Asp Arg Glu Val Leu Phe Cys His Val His Leu Val
245 250 255

Ser Ile Phe Leu Ser Ala Leu Asn Ser Ser Ala Asn Pro Ile Ile Tyr
260 265 270

Phe Phe Val Gly Ser Phe Arg Gln Arg Gln Asn Arg Gln Asn Leu Lys
275 280 285

Leu Val Leu Gln Arg Ala Leu Gln Asp Ala Ser Glu Val Asp Glu Gly
290 295 300

Gly Gly Gln Leu Pro Glu Glu Ile Leu Glu Leu Ser Gly Ser Arg Leu
305 310 315 320

Glu Gln

<210> 21
<211> 1305

<212> DNA
 <213> Homo sapiens

<400> 21
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 agccgcgcg tccgccttgt gttcctgggg gtcatcctgg tggtggcggt ggcaggcaac 180
 accacagtgc tgtgccgcct gtgcggcggc ggcgggcct gggcgggccc caagcgtcgc 240
 aagatggact tcctgcttgt gcagctggcc ctggcggacc tgcacgcgtg cgggggcacg 300
 gcgctgtcac agctggcctg ggaactgctg ggcgagccccc ggcggccac gggggacctg 360
 gctgcgtcactg tcctgcagct gctgcaggca tccgggcccc ggcgcctggc ccacctcg 420
 gtcgtcatcg ccctcgagcg cggcgcgcg gtgcgtcttc cgcacggccg ggcgcgtccc 480
 ggcgcgtgccc tcgcgcgcct gggctggctg ctggcaactgc tgctggcgct gccccggcc 540
 ttcgtggtgc gcggggactc cccctgcgcg ctgcccgcgc cgcgcgcgc aacgtccctg 600
 cagccaggcg cgcccccggc cgccgcgc tggccgggg agcgtcgctg ccacgggatc 660
 ttcgcgcgcc tcgcgcgtg gcacctgcag gtctacgcgt tctacgaggc cgtcgccggc 720
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 cggcaccggc cgcaaggcccc cgcgctgca gcgcgcgtt cggcgagccc aggtcgagcc 840
 cctgcgcggca gcgcgcgtcc cgcgcgcctt gtgcagagcc tgaagatgag cctgcgtctg 900
 ggcgcgtctgt tcgtgggctg cgagctgcct tactttgcgc cccggctggc ggccgcgtgg 960
 tcgtccgggc cgcgggaga ctgggaggga gagggcctgt cggcggcgct ggcgcgtgg 1020
 ggcgcgtggca acagcgctct caatcccttc gtctaccttc tcttccaggc gggcactgc 1080
 cggctccggc gacagctgcg gaagcggtcg ggctctctgt gtcgcgcgc gcaggaggc 1140
 gcgaggacg aggagggcc cggggccac caggcgctct accgcacaacg ctggcccccac 1200
 cctcattatc accatgctcg gcggaaaccg ctggacgagg gcggcttgcg cccacccct 1260
 ccgcgcggca gacccctgcc ttgctcctgc gaaagtgcct tctag 1305

<210> 22
 <211> 434
 <212> PRT
 <213> Homo sapiens

<400> 22
 Met Glu Asp Leu Phe Ser Pro Ser Ile Leu Pro Pro Ala Pro Asn Ile
 1 5 10 15
 Ser Val Pro Ile Leu Leu Gly Trp Gly Leu Asn Leu Thr Leu Gly Gln
 20 25 30
 Gly Ala Pro Ala Ser Gly Pro Pro Ser Arg Arg Val Arg Leu Val Phe
 35 40 45

Leu Gly Val Ile Leu Val Val Ala Val Ala Gly Asn Thr Thr Val Leu
50 55 60

Cys Arg Leu Cys Gly Gly Gly Pro Trp Ala Gly Pro Lys Arg Arg
65 70 75 80

Lys Met Asp Phe Leu Leu Val Gln Leu Ala Leu Ala Asp Leu Tyr Ala
85 90 95

Cys Gly Gly Thr Ala Leu Ser Gln Leu Ala Trp Glu Leu Leu Gly Glu
100 105 110

Pro Arg Ala Ala Thr Gly Asp Leu Ala Cys Arg Phe Leu Gln Leu Leu
115 120 125

Gln Ala Ser Gly Arg Gly Ala Ser Ala His Leu Val Val Leu Ile Ala
130 135 140

Leu Glu Arg Arg Arg Ala Val Arg Leu Pro His Gly Arg Pro Leu Pro
145 150 155 160

Ala Arg Ala Leu Ala Ala Leu Gly Trp Leu Leu Ala Leu Leu Ala
165 170 175

Leu Pro Pro Ala Phe Val Val Arg Gly Asp Ser Pro Ser Pro Leu Pro
180 185 190

Pro Pro Pro Pro Pro Thr Ser Leu Gln Pro Gly Ala Pro Pro Ala Ala
195 200 205

Arg Ala Trp Pro Gly Glu Arg Arg Cys His Gly Ile Phe Ala Pro Leu
210 215 220

Pro Arg Trp His Leu Gln Val Tyr Ala Phe Tyr Glu Ala Val Ala Gly
225 230 235 240

Phe Val Ala Pro Val Thr Val Leu Gly Val Ala Cys Gly His Leu Leu
245 250 255

Ser Val Trp Trp Arg His Arg Pro Gln Ala Pro Ala Ala Ala Pro
260 265 270

Trp Ser Ala Ser Pro Gly Arg Ala Pro Ala Pro Ser Ala Leu Pro Arg
275 280 285

Ala Lys Val Gln Ser Leu Lys Met Ser Leu Leu Leu Ala Leu Leu Phe
290 295 300

Val Gly Cys Glu Leu Pro Tyr Phe Ala Ala Arg Leu Ala Ala Ala Trp
305 310 315 320

Ser Ser Gly Pro Ala Gly Asp Trp Glu Gly Glu Gly Leu Ser Ala Ala
325 330 335

Leu Arg Val Val Ala Met Ala Asn Ser Ala Leu Asn Pro Phe Val Tyr
340 345 350

Leu Phe Phe Gln Ala Gly Asp Cys Arg Leu Arg Arg Gln Leu Arg Lys
355 360 365

Arg Leu Gly Ser Leu Cys Cys Ala Pro Gln Gly Gly Ala Glu Asp Glu
370 375 380

Glu Gly Pro Arg Gly His Gln Ala Leu Tyr Arg Gln Arg Trp Pro His
385 390 395 400

Pro His Tyr His His Ala Arg Arg Glu Pro Leu Asp Glu Gly Gly Leu
 405 410 415

Arg Pro Pro Pro Pro Arg Pro Arg Pro Leu Pro Cys Ser Cys Glu Ser
 420 425 430

Ala Phe

<210> 23
 <211> 1041
 <212> DNA
 <213> Homo sapiens

<400> 23
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 ctgctcattg tggcctttgt gctggggcgca ctaggaatg gggtcgcctt gtgtggttc 120
 tgcttccaca tgaagacactg gaagcccgac actgtttacc tttcaattt ggccgtggct 180
 gatttcctcc ttatgatctg cctgcctttt cggacagactt attaccttag acgttagacac 240
 tgggcttttgg gggacattcc ctgcccggatg gggctttca cggtggccat gaacaggccc 300
 gggagcatcg tggttcattac ggtgggtggct gcggacaggtt atttcaaaatg ggtccacccc 360
 caccacgccc tgaacactat ctccacccgg gtggcggctg gcatcgatctg caccctgtgg 420
 gcccggatca tcctggaaac agtgtatctt ttgtggaga accatctctg cgtgcaagag 480
 acggccgtct cctgtgagag cttcatcatg gagtcggcca atggctggca tgacatcatg 540
 ttccagctgg agttctttat gcccctcgcc atcatctt tttgtccctt caagattgtt 600
 tggagcctga ggcggaggca gcagctggcc agacaggctc ggatgaagaa ggcgacccgg 660
 ttcatcatgg tggtgccat tttgttcatc acatgttacc tgcccagctg gtctgctaga 720
 ctctatcc tctggacgggt gcccctcgagt gcctgcgtatc cctctgttcca tggggccctg 780
 cacataaccc tcagcttcac ctacatgaac agcatgtgg atccccctgtt gtattatccc 840
 tcaagccccct ctttcccaa atttacaac aagctaaaaa tctgcgtct gaaacccaaag 900
 cagccaggac actaaaaaac acaaaggccc gaagagatgc caatttcgaa cctcggtcgc 960
 aggagttgca tcagtgtggc aaatagtttcaaaagccagt ctgatggca atggatccc 1020
 cacattgttgg agtggactg a 1041

<210> 24
 <211> 346
 <212> PRT
 <213> Homo sapiens

<400> 24

Met Tyr Asn Gly Ser Cys Cys Arg Ile Glu Gly Asp Thr Ile Ser Gln
 1 5 10 15

Val Met Pro Pro Leu Leu Ile Val Ala Phe Val Leu Gly Ala Leu Gly
 20 25 30

Asn Gly Val Ala Leu Cys Gly Phe Cys Phe His Met Lys Thr Trp Lys
 35 40 45
 Pro Ser Thr Val Tyr Leu Phe Asn Leu Ala Val Ala Asp Phe Leu Leu
 50 55 60
 Met Ile Cys Leu Pro Phe Arg Thr Asp Tyr Tyr Leu Arg Arg Arg His
 65 70 75 80
 Trp Ala Phe Gly Asp Ile Pro Cys Arg Val Gly Leu Phe Thr Leu Ala
 85 90 95
 Met Asn Arg Ala Gly Ser Ile Val Phe Leu Thr Val Val Ala Ala Asp
 100 105 110
 Arg Tyr Phe Lys Val Val His Pro His His Ala Val Asn Thr Ile Ser
 115 120 125
 Thr Arg Val Ala Ala Gly Ile Val Cys Thr Leu Trp Ala Leu Val Ile
 130 135 140
 Leu Gly Thr Val Tyr Leu Leu Leu Glu Asn His Leu Cys Val Gln Glu
 145 150 155 160
 Thr Ala Val Ser Cys Glu Ser Phe Ile Met Glu Ser Ala Asn Gly Trp
 165 170 175
 His Asp Ile Met Phe Gln Leu Glu Phe Phe Met Pro Leu Gly Ile Ile
 180 185 190
 Leu Phe Cys Ser Phe Lys Ile Val Trp Ser Leu Arg Arg Gln Gln
 195 200 205
 Leu Ala Arg Gln Ala Arg Met Lys Lys Ala Thr Arg Phe Ile Met Val
 210 215 220
 Val Ala Ile Val Phe Ile Thr Cys Tyr Leu Pro Ser Val Ser Ala Arg
 225 230 235 240
 Leu Tyr Phe Leu Trp Thr Val Pro Ser Ser Ala Cys Asp Pro Ser Val
 245 250 255
 His Gly Ala Leu His Ile Thr Leu Ser Phe Thr Tyr Met Asn Ser Met
 260 265 270
 Leu Asp Pro Leu Val Tyr Tyr Phe Ser Ser Pro Ser Phe Pro Lys Phe
 275 280 285
 Tyr Asn Lys Leu Lys Ile Cys Ser Leu Lys Pro Lys Gln Pro Gly His
 290 295 300
 Ser Lys Thr Gln Arg Pro Glu Glu Met Pro Ile Ser Asn Leu Gly Arg
 305 310 315 320
 Arg Ser Cys Ile Ser Val Ala Asn Ser Phe Gln Ser Gln Ser Asp Gly
 325 330 335
 Gln Trp Asp Pro His Ile Val Glu Trp His
 340 345
 <210> 25
 <211> 1011
 <212> DNA
 <213> Homo sapiens

<400> 25
 atgaacaaca atacaacatg tattcaacca tctatgatct cttccatggc tttaccaatc 60
 attacatcc tcctttgtat tttgggttt ttggaaaca ctctctctca atggatattt 120
 ttaacaaaaa tagttaaaaa aacatcaacg cacatctacc tgtcacacct tgtgactgca 180
 aacttactg tgtgcagtgc catgccttc atgagtatct atttcctgaa aggttccaa 240
 tggaatatac aatctgctca atgcagatgt gtcattttc tggaaactct atccatgcat 300
 gcaagtatgt ttgtcagttt cttatattta agttggattt ccataagccg ctatgtacc 360
 ttaatgcaaa aggattccctc gcaagagact acattcatgct atgagaaaaat attttatggc 420
 catttactga aaaaatttcg ccagccaaac tttgctagaa aactatgcat ttacatatgg 480
 ggagttgtac tgggcataat catttcagg accgtatact actcagtcat agaggctaca 540
 gaaggagaag agagccatg ctacaatccg cagatggAAC taggagccat gatctctcag 600
 attgcaggtc tcatttggAAC cacatttattt ggattttcct ttttagtagt actaacatca 660
 tactactctt ttgttaagcca tctgagaaaa ataagaacct gtacgtccat tatggagaaa 720
 gatttgactt acagttctgt gaaaagacat cttttggcata tccagattct actaataagtt 780
 tgcttccttc cttatagat ttttaaaccctt atttttatg ttctacacca aagagataac 840
 tgcagcaat tgaattttt aatagaaaaca aaaaacattt tcacctgtct tgcttcggcc 900
 agaagtagca cagaccccat tatatttctt ttatttagata aaacattcaa gaagacacta 960
 tataatctctt ttacaaagtc taatttcagca catatgcaat catatggttt a 1011

<210> 26
 <211> 336
 <212> PRT
 <213> Homo sapiens

<400> 26

Met	Asn	Asn	Asn	Thr	Thr	Cys	Ile	Gln	Pro	Ser	Met	Ile	Ser	Ser	Met
1															
															15
Ala	Leu	Pro	Ile	Ile	Tyr	Ile	Leu	Leu	Cys	Ile	Val	Gly	Val	Phe	Gly
															30
Asn	Thr	Leu	Ser	Gln	Trp	Ile	Phe	Leu	Thr	Lys	Ile	Gly	Lys	Lys	Thr
															45
Ser	Thr	His	Ile	Tyr	Leu	Ser	His	Leu	Val	Thr	Ala	Asn	Leu	Leu	Val
															50
Cys	Ser	Ala	Met	Pro	Phe	Met	Ser	Ile	Tyr	Phe	Leu	Lys	Gly	Phe	Gln
															60
															75
Trp	Glu	Tyr	Gln	Ser	Ala	Gln	Cys	Arg	Val	Val	Asn	Phe	Leu	Gly	Thr
															80
															95
Leu	Ser	Met	His	Ala	Ser	Met	Phe	Val	Ser	Leu	Leu	Ile	Leu	Ser	Trp
															100
															105
															110

Ile Ala Ile Ser Arg Tyr Ala Thr Leu Met Gln Lys Asp Ser Ser Gln
 115 120 125
 Glu Thr Thr Ser Cys Tyr Glu Lys Ile Phe Tyr Gly His Leu Leu Lys
 130 135 140
 Lys Phe Arg Gln Pro Asn Phe Ala Arg Lys Leu Cys Ile Tyr Ile Trp
 145 150 155 160
 Gly Val Val Leu Gly Ile Ile Pro Val Thr Val Tyr Tyr Ser Val
 165 170 175
 Ile Glu Ala Thr Glu Gly Glu Ser Leu Cys Tyr Asn Arg Gln Met
 180 185 190
 Glu Leu Gly Ala Met Ile Ser Gln Ile Ala Gly Leu Ile Gly Thr Thr
 195 200 205
 Phe Ile Gly Phe Ser Phe Leu Val Val Leu Thr Ser Tyr Tyr Ser Phe
 210 215 220
 Val Ser His Leu Arg Lys Ile Arg Thr Cys Thr Ser Ile Met Glu Lys
 225 230 235 240
 Asp Leu Thr Tyr Ser Ser Val Lys Arg His Leu Leu Val Ile Gln Ile
 245 250 255
 Leu Leu Ile Val Cys Phe Leu Pro Tyr Ser Ile Phe Lys Pro Ile Phe
 260 265 270
 Tyr Val Leu His Gln Arg Asp Asn Cys Gln Gln Leu Asn Tyr Leu Ile
 275 280 285
 Glu Thr Lys Asn Ile Leu Thr Cys Leu Ala Ser Ala Arg Ser Ser Thr
 290 295 300
 Asp Pro Ile Ile Phe Leu Leu Asp Lys Thr Phe Lys Lys Thr Leu
 305 310 315 320
 Tyr Asn Leu Phe Thr Lys Ser Asn Ser Ala His Met Gln Ser Tyr Gly
 325 330 335

<210> 27
 <211> 1014
 <212> DNA
 <213> Homo sapiens

<400> 27
 atgaatgagc cactagacta tttagcaaat gcttctgatt tccccgatta tgcagctgct 60
 ttggaaatt gcactgatga aaacatccca ctcaagatgc actacccccc tgttatttat 120
 ggcattatct tcctcgtggg atttccaggc aatgcagtag tgatatccac ttacatttc 180
 aaaatgagac cttggaagag cagcaccatc attatgctga acctggcctg cacagatctg 240
 ctgtatctga ccagcctccc cttcctgatt cactactatg ccagtggcga aaactggatc 300
 tttggagatt tcatgtgtaa gtttatccgc ttcagcttcc atttcaacct gtatagcagc 360
 atccctttcc tcacctgttt cagcatttc cgctactgtg tgatcattca cccaatgagc 420
 tgctttcca ttcacaaaac tcgatgtgca gttgtagcct gtgctgtgggt gtggatcatt 480
 tcactggtag ctgtcattcc gatgacccctc ttgatcacat caaccaacag gaccaacaga 540

tcagcctgtc tcgacacctac cagttcgat gaactcaata ctattaagtg gtacaacctg 600
 attttactg caactacttt ctgcctcccc ttgggtatag tgacactttg ctataccacg 660
 attatccaca ctctgaccca tggactgcaa actgacagct gccttaagca gaaagcacga 720
 aggctaacca ttctgtact ccttgattt tacgtatgtt ttttacccctt ccatatctt 780
 agggtcattc ggatcgaatc tcgcctgctt tcaatcagtt gttccattga gaatcagatc 840
 catgaagctt acatcgttc tagaccatta gctgctctga acaccttgg taacctgtta 900
 ctatatgtgg tggtcagcga caacttcag caggctgtct gctcaacagt gagatgcaaa 960
 gtaagcggga accttgagca agcaaagaaa attagttact caaacaaccc ttga 1014

<210> 28
 <211> 337
 <212> PRT
 <213> Homo sapiens

<400> 28

Met Asn Glu Pro Leu Asp Tyr Leu Ala Asn Ala Ser Asp Phe Pro Asp
 1 5 10 15
 Tyr Ala Ala Ala Phe Gly Asn Cys Thr Asp Glu Asn Ile Pro Leu Lys
 20 25 30
 Met His Tyr Leu Pro Val Ile Tyr Gly Ile Ile Phe Leu Val Gly Phe
 35 40 45
 Pro Gly Asn Ala Val Val Ile Ser Thr Tyr Ile Phe Lys Met Arg Pro
 50 55 60
 Trp Lys Ser Ser Thr Ile Ile Met Leu Asn Leu Ala Cys Thr Asp Leu
 65 70 75 80
 Leu Tyr Leu Thr Ser Leu Pro Phe Leu Ile His Tyr Tyr Ala Ser Gly
 85 90 95
 Glu Asn Trp Ile Phe Gly Asp Phe Met Cys Lys Phe Ile Arg Phe Ser
 100 105 110
 Phe His Phe Asn Leu Tyr Ser Ser Ile Leu Phe Leu Thr Cys Phe Ser
 115 120 125
 Ile Phe Arg Tyr Cys Val Ile Ile His Pro Met Ser Cys Phe Ser Ile
 130 135 140
 His Lys Thr Arg Cys Ala Val Val Ala Cys Ala Val Val Trp Ile Ile
 145 150 155 160
 Ser Leu Val Ala Val Ile Pro Met Thr Phe Leu Ile Thr Ser Thr Asn
 165 170 175
 Arg Thr Asn Arg Ser Ala Cys Leu Asp Leu Thr Ser Ser Asp Glu Leu
 180 185 190
 Asn Thr Ile Lys Trp Tyr Asn Leu Ile Leu Thr Ala Thr Thr Phe Cys
 195 200 205
 Leu Pro Leu Val Ile Val Thr Leu Cys Tyr Thr Thr Ile Ile His Thr

210	215	220	
Leu Thr His Gly Leu Gln Thr Asp Ser Cys Leu Lys Gln Lys Ala Arg			
225	230	235	240
Arg Leu Thr Ile Leu Leu Leu Ala Phe Tyr Val Cys Phe Leu Pro			
245	250	255	255
Phe His Ile Leu Arg Val Ile Arg Ile Glu Ser Arg Leu Leu Ser Ile			
260	265	270	270
Ser Cys Ser Ile Glu Asn Gln Ile His Glu Ala Tyr Ile Val Ser Arg			
275	280	285	285
Pro Leu Ala Ala Leu Asn Thr Phe Gly Asn Leu Leu Leu Tyr Val Val			
290	295	300	300
Val Ser Asp Asn Phe Gln Gln Ala Val Cys Ser Thr Val Arg Cys Lys			
305	310	315	320
Val Ser Gly Asn Leu Glu Gln Ala Lys Lys Ile Ser Tyr Ser Asn Asn			
325	330	335	335

Pro

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<210> 29
<211> 993
<212> DNA
<213> Homo sapiens

<400> 29
atggatccaa ccaccccgcc ctggggaaaca gaaagtacaa cagtgaatgg aaatgaccaa 60
ggcccttcttc tgctttgtgg caaggagacc ctgatcccg tcttcctgtat ccttttcatt 120
ggccctggtcg ggctggtagg aaacgggttt gtgctctggc tcctgggctt ccgcacatgcgc 180
aggAACGcct tctctgtcta cgtcctcagc ctggccgggg ccgacttcctt ctccctctgc 240
ttccagatta taaattgcct ggtgtaccc agtaacttct tctgttccat ctccatcaat 300
ttcccttagct tcttcaccac tggatgacc tggcttacc ttgcaggcct gagcatgctg 360
agcacccgtca gcaccggagcg ctgcctgtcc gtcctgtggc ccatctggta tcgcgtccgc 420
cgccccagac acctgtcagc ggtcgtgtgt gtcctgtctt gggccctgtc cctactgctg 480
agcatcttgg aaggaaagtt ctgtggcttc ttatttatgt atggtgactc tggttgggt 540
cagacatttg atttcatcac tgcagcgtgg ctgatTTTT tattcatggt tctctgtggg 600
tccagtcgtgg ccctgctggt caggatcctc tggatccca ggggtctgcc actgaccagg 660
ctgtacatgtt ccatcctgtt cacagtgtgt gtgttccccc tctgcggccct gcccTTggc 720
attcagtggt tcctaatattt atggatctgg aaggattctg atgttttattt ttgtcatatt 780
catccagttt cagttgtcct gtcatctttt aacagcgtt ccaaccccat cattttacttc 840
ttcgtgggtt cttttaggaa gcagtggcgg ctgcagcagc cgatcctcaa gctggcttc 900
cagagggttc tgcaggacat tgctgagggtt gatcagcgtt aaggatgctt ccgtcagggc 960
accccgaga tgctgagaag cagtctgggtt tag 993

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<210> 30
<211> 330
<212> PRT
<213> Homo sapiens

<400> 30

Met Asp Pro Thr Thr Pro Ala Trp Gly Thr Glu Ser Thr Thr Val Asn
1 5 10 15

Gly Asn Asp Gln Ala Leu Leu Leu Cys Gly Lys Glu Thr Leu Ile
20 25 30

Pro Val Phe Leu Ile Leu Phe Ile Ala Leu Val Gly Leu Val Gly Asn
35 40 45

Gly Phe Val Leu Trp Leu Leu Gly Phe Arg Met Arg Arg Asn Ala Phe
50 55 60

Ser Val Tyr Val Leu Ser Leu Ala Gly Ala Asp Phe Leu Phe Leu Cys
65 70 75 80

Phe Gln Ile Ile Asn Cys Leu Val Tyr Leu Ser Asn Phe Phe Cys Ser
85 90 95

Ile Ser Ile Asn Phe Pro Ser Phe Phe Thr Thr Val Met Thr Cys Ala
100 105 110

Tyr Leu Ala Gly Leu Ser Met Leu Ser Thr Val Ser Thr Glu Arg Cys
115 120 125

Leu Ser Val Leu Trp Pro Ile Trp Tyr Arg Cys Arg Arg Pro Arg His
130 135 140

Leu Ser Ala Val Val Cys Val Leu Leu Trp Ala Leu Ser Leu Leu Leu
145 150 155 160

Ser Ile Leu Glu Gly Lys Phe Cys Gly Phe Leu Phe Ser Asp Gly Asp
165 170 175

Ser Gly Trp Cys Gln Thr Phe Asp Phe Ile Thr Ala Ala Trp Leu Ile
180 185 190

Phe Leu Phe Met Val Leu Cys Gly Ser Ser Leu Ala Leu Leu Val Arg
195 200 205

Ile Leu Cys Gly Ser Arg Gly Leu Pro Leu Thr Arg Leu Tyr Leu Thr
210 215 220

Ile Leu Leu Thr Val Leu Val Phe Leu Leu Cys Gly Leu Pro Phe Gly
225 230 235 240

Ile Gln Trp Phe Leu Ile Leu Trp Ile Trp Lys Asp Ser Asp Val Leu
245 250 255

Phe Cys His Ile His Pro Val Ser Val Val Leu Ser Ser Leu Asn Ser
260 265 270

Ser Ala Asn Pro Ile Ile Tyr Phe Phe Val Gly Ser Phe Arg Lys Gln
275 280 285

Trp Arg Leu Gln Gln Pro Ile Leu Lys Leu Ala Leu Gln Arg Ala Leu
290 295 300

Gln Asp Ile Ala Glu Val Asp His Ser Glu Gly Cys Phe Arg Gln Gly
 305 310 315 320

Thr Pro Glu Met Ser Arg Ser Ser Leu Val
 325 330

<210> 31
 <211> 1092
 <212> DNA
 <213> Homo sapiens

<400> 31
 atggggcccg gcgaggcgct gctggcggt ctccctggta tggtaactggc cgtggcgctg 60
 cstatccaacg cactggtgct gctttgtgc gcctacagcg ctgagctccg cactcgagcc 120
 tcaggcgctcc tcctggtaa tctgtcgctg ggcacacctgc tgctggcgcc gctggacatg 180
 cccttcacgc tgctcggtgt gatgcgcggg cggacaccgt cggcgcccg cgcacatgcca 240
 gtcattggct tcctggacac cttccctggcg tccaacgcgg cgctgagcgt ggcggcgctg 300
 agcgcagacc agtggctggc agtggcttc ccactgcgct acgcccggacg cctgcgaccg 360
 cgctatgcgg gcctgtgtct gggctgtgcc tggggacagt cgctggcctt ctcaggcgct 420
 gcacttggct gctcgtggct tggctacagc agcgccttcg cgtcctgttc gctgcgcctg 480
 ccgccccgagc ctgagcgtcc ggcgttcgca gccttcaccg ccacgcgtcca tgccgtggc 540
 ttcgtgctgc cgctggcggt gctctgcctc acctcgctcc aggtgcacccg ggtggcacgc 600
 agccactgcc agcgcatgga caccgtcacc atgaaggcgc tcgcgtgtct cgccgacactg 660
 caccggcactg tgccggcagcg ctgcctcattc cagcagaagc ggcgcggcca ccgcgcacc 720
 aggaagattt gcattgttat tgccgacattc ctcatctgtct ttgccccgtt tgtcatgacc 780
 aggctggcgg agctcgtgcc cttcgtcacc gtgaacgcggc agtggggcat cctcagcaag 840
 tgccctgaccc acagcaaggc ggtggccgac ccgttcacgt actctctgtct ccgcggccg 900
 ttcccgccaag tcctggccgg catggtgac cggctgctga agagaacccc ggcggccagca 960
 tccacccatg acagctctt ggtgtggcc ggcgtgggc accagctgtct gaagagaacc 1020
 ccgcggccag cgtccaccca caacggctct gtggacacag agaatgattc ctgcctgcag 1080
 cagacacact ga 1092

<210> 32
 <211> 363
 <212> PRT
 <213> Homo sapiens

<400> 32

Met Gly Pro Gly Glu Ala Leu Leu Ala Gly Leu Leu Val Met Val Leu
 1 5 10 15
 Ala Val Ala Leu Leu Ser Asn Ala Leu Val Leu Leu Cys Cys Ala Tyr
 20 25 30

Ser Ala Glu Leu Arg Thr Arg Ala Ser Gly Val Leu Leu Val Asn Leu
35 40 45

Ser Leu Gly His Leu Leu Leu Ala Ala Leu Asp Met Pro Phe Thr Leu
50 55 60

Leu Gly Val Met Arg Gly Arg Thr Pro Ser Ala Pro Gly Ala Cys Gln
65 70 75 80

Val Ile Gly Phe Leu Asp Thr Phe Leu Ala Ser Asn Ala Ala Leu Ser
85 90 95

Val Ala Ala Leu Ser Ala Asp Gln Trp Leu Ala Val Gly Phe Pro Leu
100 105 110

Arg Tyr Ala Gly Arg Leu Arg Pro Arg Tyr Ala Gly Leu Leu Gly
115 120 125

Cys Ala Trp Gly Gln Ser Leu Ala Phe Ser Gly Ala Ala Leu Gly Cys
130 135 140

Ser Trp Leu Gly Tyr Ser Ser Ala Phe Ala Ser Cys Ser Leu Arg Leu
145 150 155 160

Pro Pro Glu Pro Glu Arg Pro Arg Phe Ala Ala Phe Thr Ala Thr Leu
165 170 175

His Ala Val Gly Phe Val Leu Pro Leu Ala Val Leu Cys Leu Thr Ser
180 185 190

Leu Gln Val His Arg Val Ala Arg Ser His Cys Gln Arg Met Asp Thr
195 200 205

Val Thr Met Lys Ala Leu Ala Leu Leu Ala Asp Leu His Pro Ser Val
210 215 220

Arg Gln Arg Cys Leu Ile Gln Gln Lys Arg Arg Arg His Arg Ala Thr
225 230 235 240

Arg Lys Ile Gly Ile Ala Ile Ala Thr Phe Leu Ile Cys Phe Ala Pro
245 250 255

Tyr Val Met Thr Arg Leu Ala Glu Leu Val Pro Phe Val Thr Val Asn
260 265 270

Ala Gln Trp Gly Ile Leu Ser Lys Cys Leu Thr Tyr Ser Lys Ala Val
275 280 285

Ala Asp Pro Phe Thr Tyr Ser Leu Leu Arg Arg Pro Phe Arg Gln Val
290 295 300

Leu Ala Gly Met Val His Arg Leu Leu Lys Arg Thr Pro Arg Pro Ala
305 310 315 320

Ser Thr His Asp Ser Ser Leu Asp Val Ala Gly Met Val His Gln Leu
325 330 335

Leu Lys Arg Thr Pro Arg Pro Ala Ser Thr His Asn Gly Ser Val Asp
340 345 350

Thr Glu Asn Asp Ser Cys Leu Gln Gln Thr His
355 360

<210> 33
<211> 1125

<212> DNA
 <213> Homo sapiens

<400> 33
 atgcccacac tcaatacttc tgcctctcca cccacattct tctgggccaa tgcctccgga 60
 ggcagtgtgc tgagtgtcga tgatgtccg atgcctgtca aattccttagc cctgaggctc 120
 atggttgccc tggcctatgg gcttggggg gccattggct tgctggaaa tttggcggtg 180
 ctgtgggtac tgagtaactg tgccggaga gcccctggcc cacttcaga cacttcgtc 240
 ttcaacctgg ctctggcgga cctggactg gcactcactc tccccctttg ggcagccgag 300
 tcggcactgg actttcactg gcccctcgga ggtgcccctg gcaagatgg tctgacggcc 360
 actgtcctca acgtctatgc cagcatcttc ctcatcacag cgctgagcgt tgctcgctac 420
 tgggtggtgg ccatggctgc gggccaggc acccaccctct cactttctg ggcggaaata 480
 gcccaccctgg cagtgtggc ggcggctgcc ctggtgacgg tgcccacagc tgtttcggg 540
 gtggagggtg aggtgtgtgg tgtgcgcctt tgctgctgc gtttccccag caggtactgg 600
 ctgggggcctt accagctgca gagggtggtg ctggcttca tggccctt gggcgtcatc 660
 accaccagct acctgctgct gctggccttc ctgcagcggc ggcaacggcg gcccggaggac 720
 agcagggtcg tggcccgctc tgtccgcate ctggtggtt cttcttcct ctgctggtt 780
 ccccaaccatg tggtcactct ctgggtgtc ctggtgaaat ttgacctggt gcccggaaac 840
 agtactttct atactatcca gacgtatgtc ttccctgtca ctacttgctt ggcacacagc 900
 aatagctgcc tcaaccctgt gctgtactgt ctccctgaggc gggagccccc gcaggctctg 960
 gcaggcacct tcagggatct gcggtcgagg ctgtggccccc agggcggagg ctgggtgcaa 1020
 caggtggccc taaagcaggt aggcaggcgg tgggtcgcaa gcaacccccc ggagagccgc 1080
 cttctaccc tgctcaccaa cctggacaga gggacaccccg ggtga 1125

<210> 34
 <211> 374
 <212> PRT
 <213> Homo sapiens

<400> 34

Met	Pro	Thr	Leu	Asn	Thr	Ser	Ala	Ser	Pro	Pro	Thr	Phe	Phe	Trp	Ala
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Asn	Ala	Ser	Gly	Gly	Ser	Val	Leu	Ser	Ala	Asp	Asp	Ala	Pro	Met	Pro
			20					25					30		
Val	Lys	Phe	Leu	Ala	Leu	Arg	Leu	Met	Val	Ala	Leu	Ala	Tyr	Gly	Leu
								35					45		
Val	Gly	Ala	Ile	Gly	Leu	Leu	Gly	Asn	Leu	Ala	Val	Leu	Trp	Val	Leu
								50					60		
Ser	Asn	Cys	Ala	Arg	Arg	Ala	Pro	Gly	Pro	Pro	Ser	Asp	Thr	Phe	Val
								65					75		80

Phe Asn Leu Ala Leu Ala Asp Leu Gly Leu Ala Leu Thr Leu Pro Phe
 85 90 95
 Trp Ala Ala Glu Ser Ala Leu Asp Phe His Trp Pro Phe Gly Gly Ala
 100 105 110
 Leu Cys Lys Met Val Leu Thr Ala Thr Val Leu Asn Val Tyr Ala Ser
 115 120 125
 Ile Phe Leu Ile Thr Ala Leu Ser Val Ala Arg Tyr Trp Val Val Ala
 130 135 140
 Met Ala Ala Gly Pro Gly Thr His Leu Ser Leu Phe Trp Ala Arg Ile
 145 150 155 160
 Ala Thr Leu Ala Val Trp Ala Ala Ala Leu Val Thr Val Pro Thr
 165 170 175
 Ala Val Phe Gly Val Glu Gly Glu Val Cys Gly Val Arg Leu Cys Leu
 180 185 190
 Leu Arg Phe Pro Ser Arg Tyr Trp Leu Gly Ala Tyr Gln Leu Gln Arg
 195 200 205
 Val Val Leu Ala Phe Met Val Pro Leu Gly Val Ile Thr Thr Ser Tyr
 210 215 220
 Leu Leu Leu Ala Phe Leu Gln Arg Arg Gln Arg Arg Arg Gln Asp
 225 230 235 240
 Ser Arg Val Val Ala Arg Ser Val Arg Ile Leu Val Ala Ser Phe Phe
 245 250 255
 Leu Cys Trp Phe Pro Asn His Val Val Thr Leu Trp Gly Val Leu Val
 260 265 270
 Lys Phe Asp Leu Val Pro Trp Asn Ser Thr Phe Tyr Thr Ile Gln Thr
 275 280 285
 Tyr Val Phe Pro Val Thr Thr Cys Leu Ala His Ser Asn Ser Cys Leu
 290 295 300
 Asn Pro Val Leu Tyr Cys Leu Leu Arg Arg Glu Pro Arg Gln Ala Leu
 305 310 315 320
 Ala Gly Thr Phe Arg Asp Leu Arg Ser Arg Leu Trp Pro Gln Gly Gly
 325 330 335
 Gly Trp Val Gln Gln Val Ala Leu Lys Gln Val Gly Arg Arg Trp Val
 340 345 350
 Ala Ser Asn Pro Arg Glu Ser Arg Pro Ser Thr Leu Leu Thr Asn Leu
 355 360 365
 Asp Arg Gly Thr Pro Gly
 370
 <210> 35
 <211> 1092
 <212> DNA
 <213> Homo sapiens
 <400> 35
 atgaatcggc accatctgca ggatcacttt ctggaaatag acaagaagaa ctgctgtgtg 60

ttccgagatg acttcattgt caagggttg ccgcgggtgt tggggctgga gtttatcttc	120
gggcttctgg gcaatggcct tgccctgtgg attttctgtt tccacctcaa gtcctggaaa	180
tccagccgga tttcctgtt caacctggca gtggctgact ttctactgat catctgcctg	240
cccttcctga tggacaacta tgtgaggcgt tggactgga agtttgggaa catcccttgc	300
cggctgatgc tcttcatgtt ggctatgaac cgccaggcga gcatcatctt cctcacggtg	360
gtggcggtag acaggtattt cgggtggc catccccacc acgcccgtaa caagatctcc	420
aatcggacag cagccatcat ctcttgcctt ctgtgggca tcactattgg cctgacagtc	480
cacccctcctga agaagaagat gccgatccag aatggcggtg caaatttgcg cagcagcttc	540
agcatctgcc ataccccca gtggcacgaa gccatgttcc tcctggagtt ctccctgccc	600
ctgggcatac tcctgttctg ctcagccaga attatctgga gcctgcggca gagacaatg	660
gaccggcatg ccaagatcaa gagagccatc accttcatca tggtggtggc catcgcttt	720
gtcatctgct tccttccag cgtgggtgtg cgatccgca tcttctggct cctgcacact	780
tcgggcacgc agaattgtga agtgtaccgc tcggtgacc tggcgttctt tatcactctc	840
agttcacct acatgaacag catgctggac cccgtgggtg actacttctc cagcccatcc	900
tttcccaact tcttctccac tttgatcaac cgctgcctcc agaggaagat gacaggtgag	960
ccagataata accgcagcac gagcgtcgag ctcacagggg accccaacaa aaccagaggc	1020
gctccagagg cgtaatggc caactccgtt gagccatgga gccccttta tctggccca	1080
acctctcctt aa	1092

<210> 36
 <211> 363
 <212> PRT
 <213> Homo sapiens

<400> 36

Met Asn Arg His His Leu Gln Asp His Phe Leu Glu Ile Asp Lys Lys			
1	5	10	15
Asn Cys Cys Val Phe Arg Asp Asp Phe Ile Val Lys Val Leu Pro Pro			
20	25	30	
Val Leu Gly Leu Glu Phe Ile Phe Gly Leu Leu Gly Asn Gly Leu Ala			
35	40	45	
Leu Trp Ile Phe Cys Phe His Leu Lys Ser Trp Lys Ser Ser Arg Ile			
50	55	60	
Phe Leu Phe Asn Leu Ala Val Ala Asp Phe Leu Leu Ile Ile Cys Leu			
65	70	75	80
Pro Phe Leu Met Asp Asn Tyr Val Arg Arg Trp Asp Trp Lys Phe Gly			
85	90	95	
Asp Ile Pro Cys Arg Leu Met Leu Phe Met Leu Ala Met Asn Arg Gln			
100	105	110	

Gly Ser Ile Ile Phe Leu Thr Val Val Ala Val Asp Arg Tyr Phe Arg
 115 120 125
 Val Val His Pro His His Ala Leu Asn Lys Ile Ser Asn Arg Thr Ala
 130 135 140
 Ala Ile Ile Ser Cys Leu Leu Trp Gly Ile Thr Ile Gly Leu Thr Val
 145 150 155 160
 His Leu Leu Lys Lys Lys Met Pro Ile Gln Asn Gly Gly Ala Asn Leu
 165 170 175
 Cys Ser Ser Phe Ser Ile Cys His Thr Phe Gln Trp His Glu Ala Met
 180 185 190
 Phe Leu Leu Glu Phe Phe Leu Pro Leu Gly Ile Ile Leu Phe Cys Ser
 195 200 205
 Ala Arg Ile Ile Trp Ser Leu Arg Gln Arg Gln Met Asp Arg His Ala
 210 215 220
 Lys Ile Lys Arg Ala Ile Thr Phe Ile Met Val Val Ala Ile Val Phe
 225 230 235 240
 Val Ile Cys Phe Leu Pro Ser Val Val Val Arg Ile Arg Ile Phe Trp
 245 250 255
 Leu Leu His Thr Ser Gly Thr Gln Asn Cys Glu Val Tyr Arg Ser Val
 260 265 270
 Asp Leu Ala Phe Phe Ile Thr Leu Ser Phe Thr Tyr Met Asn Ser Met
 275 280 285
 Leu Asp Pro Val Val Tyr Tyr Phe Ser Ser Pro Ser Phe Pro Asn Phe
 290 295 300
 Phe Ser Thr Leu Ile Asn Arg Cys Leu Gln Arg Lys Met Thr Gly Glu
 305 310 315 320
 Pro Asp Asn Asn Arg Ser Thr Ser Val Glu Leu Thr Gly Asp Pro Asn
 325 330 335
 Lys Thr Arg Gly Ala Pro Glu Ala Leu Met Ala Asn Ser Gly Glu Pro
 340 345 350
 Trp Ser Pro Ser Tyr Leu Gly Pro Thr Ser Pro
 355 360
 <210> 37
 <211> 1044
 <212> DNA
 <213> Homo sapiens
 <400> 37
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 ctcatcagca agacaccctg catgccccaa gcagccagca acacttcctt gggcctgggg 120
 gacctcaggg tgcccagtc catgctgtac tggctttcc ttccctcaag cctgctggct 180
 gcagccacac tggctgtcag cccctgctg ctggtgacca tcctgcggaa ccaacggctg 240
 cgacaggagc cccactacct gctccggct aacatcctgc tctcagacacct ggcctacatt 300
 ctccctccaca tgctcatctc ctccagcagc ctgggtggct gggagctggg ccgcattggcc 360

tgtggcattc tcactgatgc tgtcttcgcc gcctgcacca gcaccatcct gtccttcacc	420
gccattgtgc tgcacaccta cctggcagtc atccatccac tgcgctaccc ctcccttcatg	480
tcccatgggg ctgcctggaa ggcagtggcc ctcatctggc tggtggcctg ctgcttcccc	540
acattcctta tttggctcag caagtggcag gatgcccagc tggaggagca aggagcttca	600
tacatcctac caccaagcat gggcacccag ccgggatgtg gcctcctggcattgttacc	660
tacacctcca ttctgtgcgt tctgttcctc tgcacagctc tcattgccaa ctgtttctgg	720
aggatctatg cagaggccaa gacttcaggc atctggggc agggctattc ccgggcccagg	780
ggcacccctgc tgatccactc agtgctgatc acattgtacg tgagcacagg ggtgggttgc	840
tccctggaca tggtgctgac caggtaccac cacattgact ctgggactca cacaatggctc	900
ctggcagcta acagtggaggc actcatgatc cttccccgtc ccatgctccc atacctgtac	960
ctgctccgct accggcagct gttggcattg gtccggggcc acctcccatc caggaggcac	1020
caggccatct ttaccatttc ctag	1044

<210> 38
<211> 347
<212> PRT
<213> *Homo sapiens*

<400> 38

Cys Cys Phe Pro Thr Phe Leu Ile Trp Leu Ser Lys Trp Gln Asp Ala
 180 185 190
 Gln Leu Glu Glu Gln Gly Ala Ser Tyr Ile Leu Pro Pro Ser Met Gly
 195 200 205
 Thr Gln Pro Gly Cys Gly Leu Leu Val Ile Val Thr Tyr Thr Ser Ile
 210 215 220
 Leu Cys Val Leu Phe Leu Cys Thr Ala Leu Ile Ala Asn Cys Phe Trp
 225 230 235 240
 Arg Ile Tyr Ala Glu Ala Lys Thr Ser Gly Ile Trp Gly Gln Gly Tyr
 245 250 255
 Ser Arg Ala Arg Gly Thr Leu Leu Ile His Ser Val Leu Ile Thr Leu
 260 265 270
 Tyr Val Ser Thr Gly Val Val Phe Ser Leu Asp Met Val Leu Thr Arg
 275 280 285
 Tyr His His Ile Asp Ser Gly Thr His Thr Trp Leu Leu Ala Ala Asn
 290 295 300
 Ser Glu Val Leu Met Met Leu Pro Arg Ala Met Leu Pro Tyr Leu Tyr
 305 310 315 320
 Leu Leu Arg Tyr Arg Gln Leu Leu Gly Met Val Arg Gly His Leu Pro
 325 330 335
 Ser Arg Arg His Gln Ala Ile Phe Thr Ile Ser
 340 345

<210> 39
 <211> 1023
 <212> DNA
 <213> Homo sapiens

<400> 39
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 aataaAGAGt ttgcttatca aactgccAGt gtggtagata cagtcatcct cccttccatG 120
 attgggatta tctgttcaac agggctggTT ggcaacatcc tcattgtatt cactataata 180
 agatccAGGA aaaaaACAGt ccctgacATC tatacttgca acctggctgt ggctgatttG 240
 gtccacatAG ttggaatGCC ttttcttatt caccaatggg cccgaggGGG agagtgggtG 300
 ttggggggc ctctctgcac catcatcaca tccctggata cttgtAACca atttgcctgt 360
 agtgcCATCA tgactgtaat gagtggac aggtactttG ccctcgTCCA accatttcga 420
 ctgacacgtt ggagaacaAG gtacaAGACC atccggatca atttgggcct ttggcagct 480
 tcctttatcc tggcattGCC tgcgtggTC tactcgaagg tcatcaaatt taaagacggT 540
 gttgagAGTT gtgcTTTGA tttgacatcc cctgacgatG tactctggta tacactttat 600
 ttgacgataa caacttttt tttccctcta cccttgattt tgggtgtGta tattttatt 660
 ttatgtata cttggagat gtatcaacAG aataaggatG ccagatgctG caatcccAGt 720
 gtaccaaaAC agagagtGat gaagttgaca aagatggtGc tggtgctggT ggtagtctt 780

atccctgagtg ctgcccccta tcatgtgata caactggtga acttacagat ggaacagccc	840
acactggcct tctatgtggg ttattacctc tccatctgtc tcagctatgc cagcagcagc	900
atataaccctt ttctctacat cctgctgagt ggaaatttcc agaaacgtct gcctcaaatac	960
caaagaagag cgactgagaa ggaaatcaac aatatggaa acactctgaa atcacacttt	1020
tag	1023

<210> 40
 <211> 340
 <212> PRT
 <213> Homo sapiens

<400> 40

Met Asn Pro Phe His Ala Ser Cys Trp Asn Thr Ser Ala Glu Leu Leu	
1 5 10 15	
Asn Lys Ser Trp Asn Lys Glu Phe Ala Tyr Gln Thr Ala Ser Val Val	
20 25 30	
Asp Thr Val Ile Leu Pro Ser Met Ile Gly Ile Ile Cys Ser Thr Gly	
35 40 45	
Leu Val Gly Asn Ile Leu Ile Val Phe Thr Ile Ile Arg Ser Arg Lys	
50 55 60	
Lys Thr Val Pro Asp Ile Tyr Ile Cys Asn Leu Ala Val Ala Asp Leu	
65 70 75 80	
Val His Ile Val Gly Met Pro Phe Leu Ile His Gln Trp Ala Arg Gly	
85 90 95	
Gly Glu Trp Val Phe Gly Gly Pro Leu Cys Thr Ile Ile Thr Ser Leu	
100 105 110	
Asp Thr Cys Asn Gln Phe Ala Cys Ser Ala Ile Met Thr Val Met Ser	
115 120 125	
Val Asp Arg Tyr Phe Ala Leu Val Gln Pro Phe Arg Leu Thr Arg Trp	
130 135 140	
Arg Thr Arg Tyr Lys Thr Ile Arg Ile Asn Leu Gly Leu Trp Ala Ala	
145 150 155 160	
Ser Phe Ile Leu Ala Leu Pro Val Trp Val Tyr Ser Lys Val Ile Lys	
165 170 175	
Phe Lys Asp Gly Val Glu Ser Cys Ala Phe Asp Leu Thr Ser Pro Asp	
180 185 190	
Asp Val Leu Trp Tyr Thr Leu Tyr Leu Thr Ile Thr Thr Phe Phe Phe	
195 200 205	
Pro Leu Pro Leu Ile Leu Val Cys Tyr Ile Leu Ile Leu Cys Tyr Thr	
210 215 220	
Trp Glu Met Tyr Gln Gln Asn Lys Asp Ala Arg Cys Cys Asn Pro Ser	
225 230 235 240	
Val Pro Lys Gln Arg Val Met Lys Leu Thr Lys Met Val Leu Val Leu	

245	250	255
Val Val Val Phe Ile Leu Ser Ala Ala Pro Tyr His Val Ile Gln Leu		
260	265	270
Val Asn Leu Gln Met Glu Gln Pro Thr Leu Ala Phe Tyr Val Gly Tyr		
275	280	285
Tyr Leu Ser Ile Cys Leu Ser Tyr Ala Ser Ser Ser Ile Asn Pro Phe		
290	295	300
Leu Tyr Ile Leu Leu Ser Gly Asn Phe Gln Lys Arg Leu Pro Gln Ile		
305	310	315
Gln Arg Arg Ala Thr Glu Lys Glu Ile Asn Asn Met Gly Asn Thr Leu		
325	330	335
Lys Ser His Phe		
340		

<210> 41
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <221> misc_feature
 <223> Novel Sequence

<400> 41 24
 cttgcagaca tcaccatggc agcc

<210> 42
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <221> misc_feature
 <223> Novel Sequence

<400> 42 24
 gtgatgtctc gagtactgga ctgg

<210> 43
 <211> 20
 <212> DNA
 <213> Artificial Sequence

<220>
 <221> misc_feature
 <223> Novel Sequence

<400> 43 20
 gaagctgtga agagtgtgc

<210> 44
 <211> 24
 <212> DNA

<213> Artificial Sequence

<220>

<221> misc_feature

<223> Novel Sequence

<400> 44

gtcagcaata ttgataagca gcag

24

<210> 45

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<221> misc_feature

<223> Novel Sequence

<400> 45

ccatggggaa cgattctgtc agctacg

27

<210> 46

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<221> misc_feature

<223> Novel Sequence

<400> 46

gctatgcctg aagccagtct tgtg

24

<210> 47

<211> 26

<212> DNA

<213> Artificial Sequence

<220>

<221> misc_feature

<223> Novel Sequence

<400> 47

ccaggatgtt gtgtcaccgt ggtggc

26

<210> 48

<211> 26

<212> DNA

<213> Artificial Sequence

<220>

<221> misc_feature

<223> Novel Sequence

<400> 48

cacagcgctg cagccctgca gctggc

26

<210> 49
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 49
cttcctctcg tagggatgaa ccagac

26

<210> 50
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
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<223> Novel Sequence

<400> 50
ctcgcacagg tgggaaggcac ctgtgg

26

<210> 51
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 51
gcctgtgaca ggaggtaccc tgg

23

<210> 52
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 52
catatccctc cgagtgtcca gcgcc

25

<210> 53
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature

<223> Novel Sequence

<400> 53 31
gcatggagag aaaattttagt cccttgcaac c

<210> 54
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 54 27
caagaacagg tctcatctaa gagctcc

<210> 55
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 55 26
gctgttgcca tgacgtccac ctgcac

<210> 56
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 56 26
ggacagttca aggtttgcct tagaac

<210> 57
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 57 23
ctttcgatac tgctcctatg ctc

<210> 58
<211> 26

<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 58
gtagtccact gaaagtccag tgatcc

26

<210> 59
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 59
tttctgagca tggatccaac catctc

26

<210> 60
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 60
ctgtctgaca gggcagagggc tcttc

25

<210> 61
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 61
ggaactcgta tagaccaggc gtcgctcc

28

<210> 62
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 62

28

ggaggttgcg ccttagcgac agatgacc

<210> 63
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 63
ctgcacccgg acacttgctc tg

22

<210> 64
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 64
gtctgcttgt tcagtgccac tcaac

25

<210> 65
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 65
tatctgcaat tctattctag ctcctg

26

<210> 66
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 66
tgccctaat aaagtcacat gaatgc

26

<210> 67
<211> 23
<212> DNA
<213> Artificial Sequence

<220>

<221> misc_feature
<223> Novel Sequence

<400> 67
ggagacaacc atgaatgagc cac

23

<210> 68
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 68
tatttcaagg gttgtttgag taac

24

<210> 69
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 69
ggcaccagtg gaggtttct gagcatg

27

<210> 70
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 70
ctgatggaag tagaggctgt ccatctc

27

<210> 71
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 71
cctggcgagc cgctagcgcc atg

23

<210> 72

<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 72
atgagccctg ccaggccctc agt

23

<210> 73
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 73
ctgcgatgcc cacactcaat acttctg

27

<210> 74
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 74
aaggatccta cacttgggtgg atctcag

27

<210> 75
<211> 22
<212> DNA
<213> Artificial Sequence

<400> 75
gctggagcat tcactaggcg ag

22

<210> 76
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 76
agatcctggc tcttgggtgac aatg

24

<210> 77

<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<223> Novel Sequence

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24

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<220>
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<223> Novel Sequence

<400> 78
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27

<210> 79
<211> 28
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<400> 79
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28

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<400> 80
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25

<210> 81
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<210> 83		
<211> 1356		
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<213> Homo sapiens		
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	tcggaaatctg tggcccttctt cttcatgctc ctgctggact tgactgctgt ggctggcaat	180
	gccgctgtga tggccgtat cggcaagacg cctggccctcc gaaaatttgcg cttcgcttcc	240
	cacctctgcc tggtgacact gctggctgcc ctgaccctca tgcccttgcg catgtctcc	300
	agctctgccc tctttgacca cggccctttt ggggaggtgg cctggccgcct ctacttgcgtt	360
	ctgagcgtgt gctttgtcag cctggccatc ctctcggtgt cagccatcaa tgtggagcgc	420
	tactattacg tagtccaccc catgcgtac gaggtgcgcgca tgacgctggg gctggtgcc	480
	tctgtgtgg tgggtgtgtg ggtgaaggcc ttggccatgg cttctgtgcc agtgttggga	540
	agggtctccct gggaggaagg agctccca gtcggccctcc gctgttcaact ccagtggagc	600
	cacagtgccct actgcccacgct ttttgggtgt gtctttgtg tcctttactt tctgttgc	660
	ctgctccatca tacttgggtt ctactgcacg atgttccgag tggcccggtt ggctgccc	720
	cagcacgggc cgctgcccac gtggatggag acacccggc aacgctccga atctctcagc	780
	agccgctcca cgatggtcac cagctcgaaa gccccccaga ccacccaca ccggacgttt	840
	ggggggagggaa aagcaaagggt ggttctccctg gctgtggggg gacagttccct gctctgttgg	900
	ttggccctact tcttttcca cctctatgtt gcccgtggcctt ctcagccat ttcaactggg	960
	caggtggaga gtgtggtcac ctggattggc tactttgtc tcacttccaa cccttcttc	1020
	tatggatgtc tcaaccggca gatccggggg gagctcagca agcagttgt ctgttcttc	1080
	aaggccagtc cagaggagga gctgaggctg cctagccggg agggctccat tgaggagaac	1140
	ttccctgcagt tccttcaggg gactggctgt cttctgagt cctgggttcc ccgaccccta	1200
	cccagccca agcaggagcc acctgctgtt gactttcgaa tcccaggcca gatacgctgag	1260

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ctccgtcctg ccgcctcacc ccggctggag tcatga 1356

<210> 84
<211> 451
<212> PRT
<213> Homo sapiens

<400> 84

Met Glu Ser Ser Pro Ile Pro Gln Ser Ser Gly Asn Ser Ser Thr Leu
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Gly Arg Val Pro Gln Thr Pro Gly Pro Ser Thr Ala Ser Gly Val Pro
20 25 30
Glu Val Gly Leu Arg Asp Val Ala Ser Glu Ser Val Ala Leu Phe Phe
35 40 45
Met Leu Leu Leu Asp Leu Thr Ala Val Ala Gly Asn Ala Ala Val Met
50 55 60
Ala Val Ile Ala Lys Thr Pro Ala Leu Arg Lys Phe Val Phe Val Phe
65 70 75 80
His Leu Cys Leu Val Asp Leu Leu Ala Ala Leu Thr Leu Met Pro Leu
85 90 95
Ala Met Leu Ser Ser Ser Ala Leu Phe Asp His Ala Leu Phe Gly Glu
100 105 110
Val Ala Cys Arg Leu Tyr Leu Phe Leu Ser Val Cys Phe Val Ser Leu
115 120 125
Ala Ile Leu Ser Val Ser Ala Ile Asn Val Glu Arg Tyr Tyr Tyr Val
130 135 140
Val His Pro Met Arg Tyr Glu Val Arg Met Thr Leu Gly Leu Val Ala
145 150 155 160
Ser Val Leu Val Gly Val Trp Val Lys Ala Leu Ala Met Ala Ser Val
165 170 175
Pro Val Leu Gly Arg Val Ser Trp Glu Glu Gly Ala Pro Ser Val Pro
180 185 190
Pro Gly Cys Ser Leu Gln Trp Ser His Ser Ala Tyr Cys Gln Leu Phe
195 200 205
Val Val Val Phe Ala Val Leu Tyr Phe Leu Leu Pro Leu Leu Ile
210 215 220
Leu Val Val Tyr Cys Ser Met Phe Arg Val Ala Arg Val Ala Ala Met
225 230 235 240
Gln His Gly Pro Leu Pro Thr Trp Met Glu Thr Pro Arg Gln Arg Ser
245 250 255
Glu Ser Leu Ser Ser Arg Ser Thr Met Val Thr Ser Ser Gly Ala Pro
260 265 270
Gln Thr Thr Pro His Arg Thr Phe Gly Gly Lys Ala Lys Val Val

275	280	285
Leu Leu Ala Val Gly Gly Gln Phe Leu Leu Cys Trp Leu Pro Tyr Phe		
290	295	300
Ser Phe His Leu Tyr Val Ala Leu Ser Ala Gln Pro Ile Ser Thr Gly		
305	310	315
Gln Val Glu Ser Val Val Thr Trp Ile Gly Tyr Phe Cys Phe Thr Ser		
325	330	335
Asn Pro Phe Phe Tyr Gly Cys Leu Asn Arg Gln Ile Arg Gly Glu Leu		
340	345	350
Ser Lys Gln Phe Val Cys Phe Phe Lys Pro Ala Pro Glu Glu Glu Leu		
355	360	365
Arg Leu Pro Ser Arg Glu Gly Ser Ile Glu Glu Asn Phe Leu Gln Phe		
370	375	380
Leu Gln Gly Thr Gly Cys Pro Ser Glu Ser Trp Val Ser Arg Pro Leu		
385	390	395
Pro Ser Pro Lys Gln Glu Pro Pro Ala Val Asp Phe Arg Ile Pro Gly		
405	410	415
Gln Ile Ala Glu Glu Thr Ser Glu Phe Leu Glu Gln Gln Leu Thr Ser		
420	425	430
Asp Ile Ile Met Ser Asp Ser Tyr Leu Arg Pro Ala Ala Ser Pro Arg		
435	440	445
Leu Glu Ser		
450		
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<213> Homo sapiens		
<400> 85		
caggaaggca aagaccacca tcatcatc		28
<210> 86		
<211> 28		
<212> DNA		
<213> Homo sapiens		
<400> 86		
gatgatgatg gtgggtcttg ctttcctg		28
<210> 87		
<211> 1041		
<212> DNA		
<213> Homo sapiens		
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ggcaccttca gcaataacaa cagcaggaac tgcacaattt aaaaacttcaa gagagaattt		120
ttcccaattt tataatctgat aatattttc tggggagtct tgggaaatgg gttgtccata		180

tatgtttcc	tgca	gccc	taa	gaagtcc	acat	ctgt	ga	acgtt	ttcat	gctaa	atctg	240
gccat	ttc	ag	atc	cctgtt	cata	aggc	ac	ggc	gtgact	ttat	ctt	300
ggc	tcc	aa	ttt	ggat	at	tttgg	agac	cttgg	ggact	ttat	ttt	360
aac	atgt	tac	ca	gc	ag	tttgc	tacc	gtg	ctgag	tttgc	gtt	420
gtt	caccc	ct	tc	tc	at	gtc	acc	agc	atc	agg	atc	480
atc	at	at	at	gg	at	at	at	gtt	cttgc	at	at	540
aac	ggc	at	gt	tc	at	at	at	gg	at	at	at	600
atg	aact	ata	ta	tt	tg	cc	tt	gg	ct	gt	gg	660
atc	at	at	at	gg	at	at	at	gg	at	at	at	720
tcc	ac	ag	at	gg	at	at	at	gg	at	at	at	780
ctg	cc	ct	at	at	ac	at	at	at	at	at	at	840
ctg	cc	ct	at	at	ac	at	at	at	at	at	at	900
aat	cct	ct	tc	tc	at	at	at	at	at	at	at	960
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ag	aa	aa	aa	aa	aa	aa	aa	aa	aa	aa	aa	1041

<210> 88
 <211> 346
 <212> PRT
 <213> Homo sapiens

<400> 88

Met Glu Arg Lys Phe Met Ser Leu Gln Pro Ser Ile Ser Val Ser Glu
 1 5 10 15

Met Glu Pro Asn Gly Thr Phe Ser Asn Asn Asn Ser Arg Asn Cys Thr
 20 25 30

Ile Glu Asn Phe Lys Arg Glu Phe Phe Pro Ile Val Tyr Leu Ile Ile
 35 40 45

Phe Phe Trp Gly Val Leu Gly Asn Gly Leu Ser Ile Tyr Val Phe Leu
 50 55 60

Gln Pro Tyr Lys Lys Ser Thr Ser Val Asn Val Phe Met Leu Asn Leu
 65 70 75 80

Ala Ile Ser Asp Leu Leu Phe Ile Ser Thr Leu Pro Phe Arg Ala Asp
 85 90 95

Tyr Tyr Leu Arg Gly Ser Asn Trp Ile Phe Gly Asp Leu Ala Cys Arg
 100 105 110

Ile Met Ser Tyr Ser Leu Tyr Val Asn Met Tyr Ser Ser Ile Tyr Phe
 115 120 125

Leu Thr Val Leu Ser Val Val Arg Phe Leu Ala Met Val His Pro Phe
 130 135 140

Arg Leu Leu His Val Thr Ser Ile Arg Ser Ala Trp Ile Leu Cys Gly
 145 150 155 160
 Ile Ile Trp Ile Leu Ile Met Ala Ser Ser Ile Met Leu Leu Asp Ser
 165 170 175
 Gly Ser Glu Gln Asn Gly Ser Val Thr Ser Cys Leu Glu Leu Asn Leu
 180 185 190
 Tyr Lys Ile Ala Lys Leu Gln Thr Met Asn Tyr Ile Ala Leu Val Val
 195 200 205
 Gly Cys Leu Leu Pro Phe Phe Thr Leu Ser Ile Cys Tyr Leu Leu Ile
 210 215 220
 Ile Arg Val Leu Leu Lys Val Glu Val Pro Glu Ser Gly Leu Arg Val
 225 230 235 240
 Ser His Arg Lys Ala Lys Thr Thr Ile Ile Ile Thr Leu Ile Ile Phe
 245 250 255
 Phe Leu Cys Phe Leu Pro Tyr His Thr Leu Arg Thr Val His Leu Thr
 260 265 270
 Thr Trp Lys Val Gly Leu Cys Lys Asp Arg Leu His Lys Ala Leu Val
 275 280 285
 Ile Thr Leu Ala Leu Ala Ala Asn Ala Cys Phe Asn Pro Leu Leu
 290 295 300
 Tyr Tyr Phe Ala Gly Glu Asn Phe Lys Asp Arg Leu Lys Ser Ala Leu
 305 310 315 320
 Arg Lys Gly His Pro Gln Lys Ala Lys Thr Lys Cys Val Phe Pro Val
 325 330 335
 Ser Val Trp Leu Arg Lys Glu Thr Arg Val
 340 345
 <210> 89
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 <221> misc_feature
 <223> Novel Sequence
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 <210> 90
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 <212> DNA
 <213> Artificial Sequence
 <220>
 <221> misc_feature
 <223> Novel Sequence
 <400> 90
 gaagatc_{act} ttcttagctt tgca_{act}gg 28

<210> 91
 <211> 1527
 <212> DNA
 <213> Homo sapiens

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ttcctcgccg cctcttcgt cgcaacata gtgcgtgcgc tagtgttgc ggcgaagccg	180
cagctgctgc aggtgaccaa ccgttttatac tttaacctcc tcgtcaccga cctgctgcag	240
atttcgctcg tggcccccgt ggtgggtggcc acctctgtgc ctctcttctg gcccctcaac	300
agccacttct gcacggccct ggttagcctc acccacctgt tcgccttcgc cagcgtcaac	360
accattgtcg tgggtgtcaagt ggatcgctac ttgtccatca tccaccctct ctcctacccg	420
tccaagatga cccagcgccg cggttacctg ctccctctatg gcacacctggat tgtggccatc	480
ctgcagagca ctccctccact ctacggctgg ggccaggctg cctttgtatga ggcgaatgct	540
ctctgctcca tgcgttgggg ggccagcccc agctacacta ttctcagctgt ggtgtccctc	600
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aggcagcatg ctctgctgtt caatgtcaag agacacagct tggaaagtgcg agtcaaggac	720
tgtgtggaga atgaggatga agagggagca gagaagaagg aggagttcca ggatgagagt	780
gagtttcgccc gccagcatga aggtgaggctc aaggccaagg agggcagaat ggaagccaaag	840
gacggcagcc tgaaggccaa ggaaggaagc acggggacca gtgagagtag tgttagaggcc	900
aggggcagcg aggaggtcag agagagcagc acgggtggcca ggcacggcag catggagggt	960
aaggaaggca gcaccaaagt tgaggagaac agcatgaagg cagacaaggg tcgcacagag	1020
gtcaaccagt gcagcattga ctgggtgaa gatgacatgg agtttggatga agacgacatc	1080
aatttcagtg aggtgacgt cgaggcagt aacatcccg agagcctccc acccagtcgt	1140
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tggctttct tcctgcatgt ctgcacatccac ccctatgtct atggctacat gcacaagacc	1380
atataagaagg aaatccagga catgctgaag aagttttctt gcaaggaaaa gcccccaaaa	1440
gaagatagcc acccagaccc gcccggaaaca gaggggtggga ctgaaggcaa gattgtccct	1500
tcctacgtt ctgctacttt tccttga	1527

<210> 92
 <211> 508
 <212> PRT
 <213> Homo sapiens

<400> 92

Met Thr Ser Thr Cys Thr Asn Ser Thr Arg Glu Ser Asn Ser Ser His
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Thr Cys Met Pro Leu Ser Lys Met Pro Ile Ser Leu Ala His Gly Ile
20 25 30

Ile Arg Ser Thr Val Leu Val Ile Phe Leu Ala Ala Ser Phe Val Gly
35 40 45

Asn Ile Val Leu Ala Leu Val Leu Gln Arg Lys Pro Gln Leu Leu Gln
50 55 60

Val Thr Asn Arg Phe Ile Phe Asn Leu Leu Val Thr Asp Leu Leu Gln
65 70 75 80

Ile Ser Leu Val Ala Pro Trp Val Val Ala Thr Ser Val Pro Leu Phe
85 90 95

Trp Pro Leu Asn Ser His Phe Cys Thr Ala Leu Val Ser Leu Thr His
100 105 110

Leu Phe Ala Phe Ala Ser Val Asn Thr Ile Val Val Val Ser Val Asp
115 120 125

Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr
130 135 140

Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile
145 150 155 160

Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp
165 170 175

Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr
180 185 190

Thr Ile Leu Ser Val Val Ser Phe Ile Val Ile Pro Leu Ile Val Met
195 200 205

Ile Ala Cys Tyr Ser Val Val Phe Cys Ala Ala Arg Arg Gln His Ala
210 215 220

Leu Leu Tyr Asn Val Lys Arg His Ser Leu Glu Val Arg Val Lys Asp
225 230 235 240

Cys Val Glu Asn Glu Asp Glu Glu Gly Ala Glu Lys Lys Glu Glu Phe
245 250 255

Gln Asp Glu Ser Glu Phe Arg Arg Gln His Glu Gly Glu Val Lys Ala
260 265 270

Lys Glu Gly Arg Met Glu Ala Lys Asp Gly Ser Leu Lys Ala Lys Glu
275 280 285

Gly Ser Thr Gly Thr Ser Glu Ser Ser Val Glu Ala Arg Gly Ser Glu
290 295 300

Glu Val Arg Glu Ser Ser Thr Val Ala Ser Asp Gly Ser Met Glu Gly
305 310 315 320

Lys Glu Gly Ser Thr Lys Val Glu Glu Asn Ser Met Lys Ala Asp Lys
325 330 335

Gly Arg Thr Glu Val Asn Gln Cys Ser Ile Asp Leu Gly Glu Asp Asp
340 345 350
Met Glu Phe Gly Glu Asp Asp Ile Asn Phe Ser Glu Asp Asp Val Glu
355 360 365
Ala Val Asn Ile Pro Glu Ser Leu Pro Pro Ser Arg Arg Asn Ser Asn
370 375 380
Ser Asn Pro Pro Leu Pro Arg Cys Tyr Gln Cys Lys Ala Lys Lys Val
385 390 395 400
Ile Phe Ile Ile Ile Phe Ser Tyr Val Leu Ser Leu Gly Pro Tyr Cys
405 410 415
Phe Leu Ala Val Leu Ala Val Trp Val Asp Val Glu Thr Gln Val Pro
420 425 430
Gln Trp Val Ile Thr Ile Ile Trp Leu Phe Phe Leu Gln Cys Cys
435 440 445
Ile His Pro Tyr Val Tyr Gly Tyr Met His Lys Thr Ile Lys Lys Glu
450 455 460
Ile Gln Asp Met Leu Lys Lys Phe Phe Cys Lys Glu Lys Pro Pro Lys
465 470 475 480
Glu Asp Ser His Pro Asp Leu Pro Gly Thr Glu Gly Gly Thr Glu Gly
485 490 495
Lys Ile Val Pro Ser Tyr Asp Ser Ala Thr Phe Pro
500 505

<210> 93
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<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 93 29
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<210> 94
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 94 29
gccaatcttc ctcttggcgc ggtggcggc

<210> 95
<211> 1092
<212> DNA

<213> *Homo sapiens*

<400> 95
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cccttcacgc tgctcggtgt gatgcgcggg cggacaccgt cggcgccccg cgcacatgcca 240
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gcacttggct gctcggtgt tggctacagc agcgccttcg cgtcctgttc gctgcgcctg 480
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ccgcggcccgatc cgtccacccca caacggctct gtggacacag agaatgattc ctgcctgtcag 1080
cagacacact ga 1092

<210> 96
<211> 363
<212> PRT
<213> *Homo sapiens*

<400> 96

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Ala Val Ala Leu Leu Ser Asn Ala Leu Val Leu Leu Cys Cys Ala Tyr
20 25 30

Ser Ala Glu Leu Arg Thr Arg Ala Ser Gly Val Leu Leu Val Asn Leu
35 40 45

Ser Leu Gly His Leu Leu Leu Ala Ala Leu Asp Met Pro Phe Thr Leu
50 55 60

Leu Gly Val Met Arg Gly Arg Thr Pro Ser Ala Pro Gly Ala Cys Gln
65 70 75 80

Val Ile Gly Phe Leu Asp Thr Phe Leu Ala Ser Asn Ala Ala Leu Ser
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85

90

95

Val Ala Ala Leu Ser Ala Asp Gln Trp Leu Ala Val Gly Phe Pro Leu
 100 105 110

Arg Tyr Ala Gly Arg Leu Arg Pro Arg Tyr Ala Gly Leu Leu Leu Gly
 115 120 125

Cys Ala Trp Gly Gln Ser Leu Ala Phe Ser Gly Ala Ala Leu Gly Cys
 130 135 140

Ser Trp Leu Gly Tyr Ser Ser Ala Phe Ala Ser Cys Ser Leu Arg Leu
 145 150 155 160

Pro Pro Glu Pro Glu Arg Pro Arg Phe Ala Ala Phe Thr Ala Thr Leu
 165 170 175

His Ala Val Gly Phe Val Leu Pro Leu Ala Val Leu Cys Leu Thr Ser
 180 185 190

Leu Gln Val His Arg Val Ala Arg Ser His Cys Gln Arg Met Asp Thr
 195 200 205

Val Thr Met Lys Ala Leu Ala Leu Asp Leu His Pro Ser Val
 210 215 220

Arg Gln Arg Cys Leu Ile Gln Gln Lys Arg Arg Arg His Arg Ala Thr
 225 230 235 240

Arg Lys Ile Gly Ile Ala Ile Ala Thr Phe Leu Ile Cys Phe Ala Pro
 245 250 255

Tyr Val Met Thr Arg Leu Ala Glu Leu Val Pro Phe Val Thr Val Asn
 260 265 270

Ala Gln Lys Gly Ile Leu Ser Lys Cys Leu Thr Tyr Ser Lys Ala Val
 275 280 285

Ala Asp Pro Phe Thr Tyr Ser Leu Leu Arg Arg Pro Phe Arg Gln Val
 290 295 300

Leu Ala Gly Met Val His Arg Leu Leu Lys Arg Thr Pro Arg Pro Ala
 305 310 315 320

Ser Thr His Asp Ser Ser Leu Asp Val Ala Gly Met Val His Gln Leu
 325 330 335

Leu Lys Arg Thr Pro Arg Pro Ala Ser Thr His Asn Gly Ser Val Asp
 340 345 350

Thr Glu Asn Asp Ser Cys Leu Gln Gln Thr His
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<210> 97

<211> 34

<212> DNA

<213> Artificial Sequence

<220>

<221> misc_feature

<223> Novel Sequence

<400> 97

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34

<210> 98
 <211> 36
 <212> DNA
 <213> Artificial Sequence

<220>
 <221> misc_feature
 <223> Novel Sequence

<400> 98
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36

<210> 99
 <211> 2610
 <212> DNA
 <213> Homo sapiens and Rat

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 tactattacg tagtccaccc catgcgtac gaggtgcgca tgacgctggg gctggggcc 480
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 cacagtgcct actgcccact ttttgtggt gtctttgtc tcctttactt tctgttgccc 660
 ctgtctctca tacttgtgtt ctactgcagc atgttccagtg tggcccgctg ggctgcccatt 720
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 ttggccctact tctctttcca cctctatgtt gcccgtgtt ctcagcccat ttcaactggg 960
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<212> PRT
<213> *Homo sapiens* and Rat

<400> 100

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20 25 30

Glu Val Gly Leu Arg Asp Val Ala Ser Glu Ser Val Ala Leu Phe Phe
35 40 45

Met Leu Leu Leu Asp Leu Thr Ala Val Ala Gly Asn Ala Ala Val Met
50 55 60

Ala Val Ile Ala Lys Thr Pro Ala Leu Arg Lys Phe Val Phe Val Phe
65 70 75 80

His Leu Cys Leu Val Asp Leu Leu Ala Ala Leu Thr Leu Met Pro Leu
85 90 95

Ala Met Leu Ser Ser Ser Ala Leu Phe Asp His Ala Leu Phe Gly Glu
100 105 110

Val Ala Cys Arg Leu Tyr Leu Phe Leu Ser Val Cys Phe Val Ser Leu
115 120 125

Ala Ile Leu Ser Val Ser Ala Ile Asn Val Glu Arg Tyr Tyr Tyr Val
130 135 140

Val His Pro Met Arg Tyr Glu Val Arg Met Thr Leu Gly Leu Val Ala
145 150 155 160

Ser Val Leu Val Gly Val Trp Val Lys Ala Leu Ala Met Ala Ser Val
165 170 175

Pro Val Leu Gly Arg Val Ser Trp Glu Glu Gly Ala Pro Ser Val Pro
180 185 190

Pro Gly Cys Ser Leu Gln Trp Ser His Ser Ala Tyr Cys Gln Leu Phe
195 200 205

Val Val Val Phe Ala Val Leu Tyr Phe Leu Leu Pro Leu Leu Ile
210 215 220

Leu Val Val Tyr Cys Ser Met Phe Arg Val Ala Arg Val Ala Ala Met
225 230 235 240

Gln His Gly Pro Leu Pro Thr Trp Met Glu Thr Pro Arg Gln Arg Ser
245 250 255

Glu Ser Leu Ser Ser Arg Ser Thr Met Val Thr Ser Ser Gly Ala Pro
260 265 270

Gln Thr Thr Pro His Arg Thr Phe Gly Gly Lys Ala Ala Val Val
275 280 285

Leu Leu Ala Val Gly Gly Gln Phe Leu Leu Cys Trp Leu Pro Tyr Phe
290 295 300

Ser Phe His Leu Tyr Val Ala Leu Ser Ala Gln Pro Ile Ser Thr Gly
305 310 315 320

Gln Val Glu Ser Val Val Thr Trp Ile Gly Tyr Phe Cys Phe Thr Ser
325 330 335

Asn Pro Phe Phe Tyr Gly Cys Leu Asn Arg Gln Ile Arg Gly Glu Leu
340 345 350

Ser Lys Gln Phe Val Cys Phe Phe Lys Pro Ala Pro Glu Glu Glu Leu
355 360 365

Arg Leu Pro Ser Arg Glu Gly Ser Ile Glu Glu Asn Phe Leu Gln Phe
370 375 380

Leu Gln Gly Thr Gly Cys Pro Ser Glu Ser Trp Val Ser Arg Pro Leu
385 390 395 400

Pro Ser Pro Lys Gln Glu Pro Pro Ala Val Asp Phe Arg Ile Pro Gly
405 410 415

Gln Ile Ala Glu Glu Thr Ser Glu Phe Leu Glu Gln Gln Leu Thr Ser
420 425 430

Asp Ile Ile Met Ser Asp Ser Tyr Leu Arg Pro Ala Ala Ser Pro Arg
435 440 445

Leu Glu Ser Ala Ile Ser Ala Glu Phe His His Thr Gly Leu Val Asp
450 455 460

Pro Ser Ser Val Pro Ser Leu Gly Cys Arg Ser Met Gly Cys Leu Gly
465 470 475 480

Asn Ser Lys Thr Glu Asp Gln Arg Asn Glu Glu Lys Ala Gln Arg Glu
485 490 495

Ala Asn Lys Lys Ile Glu Lys Gln Leu Gln Lys Asp Lys Gln Val Tyr
500 505 510

Arg Ala Thr His Arg Leu Leu Leu Gly Ala Gly Glu Ser Gly Lys
515 520 525

Ser Thr Ile Val Lys Gln Met Arg Ile Leu His Val Asn Gly Phe Asn
530 535 540

Gly Glu Gly Glu Glu Asp Pro Gln Ala Ala Arg Ser Asn Ser Asp
545 550 555 560

Gly Glu Lys Ala Thr Lys Val Gln Asp Ile Lys Asn Asn Leu Lys Glu
565 570 575

Ala Ile Glu Thr Ile Val Ala Ala Met Ser Asn Leu Val Pro Pro Val
580 585 590

Glu Leu Ala Asn Pro Glu Asn Gln Phe Arg Val Asp Tyr Ile Leu Ser
595 600 605

Val Met Asn Val Pro Asn Phe Asp Phe Pro Pro Glu Phe Tyr Glu His
610 615 620

Ala Lys Ala Leu Trp Glu Asp Glu Gly Val Arg Ala Cys Tyr Glu Arg
625 630 635 640

Ser Asn Glu Tyr Gln Leu Ile Asp Cys Ala Gln Tyr Phe Leu Asp Lys
645 650 655

Ile Asp Val Ile Lys Gln Ala Asp Tyr Val Pro Ser Asp Gln Asp Leu
660 665 670

Leu Arg Cys Arg Val Leu Thr Ser Gly Ile Phe Glu Thr Lys Phe Gln
675 680 685

Val Asp Lys Val Asn Phe His Met Phe Asp Val Gly Gly Gln Arg Asp
690 695 700

Glu Arg Arg Lys Trp Ile Gln Cys Phe Asn Asp Val Thr Ala Ile Ile
705 710 715 720

Phe Val Val Ala Ser Ser Tyr Asn Met Val Ile Arg Glu Asp Asn
725 730 735

Gln Thr Asn Arg Leu Gln Glu Ala Leu Asn Leu Phe Lys Ser Ile Trp
740 745 750

Asn Asn Arg Trp Leu Arg Thr Ile Ser Val Ile Leu Phe Leu Asn Lys

755	760	765
Gln Asp Leu Leu Ala Glu Lys Val Leu Ala Gly Lys Ser Lys Ile Glu		
770	775	780
Asp Tyr Phe Pro Glu Phe Ala Arg Tyr Thr Thr Pro Glu Asp Ala Thr		
785	790	795
800		
Pro Glu Pro Gly Glu Asp Pro Arg Val Thr Arg Ala Lys Tyr Phe Ile		
805	810	815
Arg Asp Glu Phe Leu Arg Ile Ser Thr Ala Ser Gly Asp Gly Arg His		
820	825	830
Tyr Cys Tyr Pro His Phe Thr Cys Ala Val Asp Thr Glu Asn Ile Arg		
835	840	845
Arg Val Phe Asn Asp Cys Arg Asp Ile Ile Gln Arg Met His Leu Arg		
850	855	860
Gln Tyr Glu Leu Leu		
865		
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ttccctcgccg cctctttcgt cggcaacata gtgctggcgc tagtggca gcgcaagccg		180
cagctgctgc aggtgaccaa ccgttttatac ttaacctcc tcgtcaccga cctgctgcag		240

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<210> 104

<211> 926

<212> PRT

<213> Homo sapiens and Rat

<400> 104

Met Thr Ser Thr Cys Thr Asn Ser Thr Arg Glu Ser Asn Ser Ser His																																																																					
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10	15																																																																				
Thr Cys Met Pro Leu Ser Lys Met Pro Ile Ser Leu Ala His Gly Ile																																																																					
20	25	30		Ile Arg Ser Thr Val Leu Val Ile Phe Leu Ala Ala Ser Phe Val Gly		35	40	45		Asn Ile Val Leu Ala Leu Val Leu Gln Arg Lys Pro Gln Leu Leu Gln		50	55	60		Val Thr Asn Arg Phe Ile Phe Asn Leu Leu Val Thr Asp Leu Leu Gln		65	70	75	80	Ile Ser Leu Val Ala Pro Trp Val Val Ala Thr Ser Val Pro Leu Phe		85	90	95		Trp Pro Leu Asn Ser His Phe Cys Thr Ala Leu Val Ser Leu Thr His		100	105	110		Leu Phe Ala Phe Ala Ser Val Asn Thr Ile Val Val Val Ser Val Asp		115	120	125		Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr		130	135	140		Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile		145	150	155	160	Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp		165	170	175		Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr		180	185	190							
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Ile Arg Ser Thr Val Leu Val Ile Phe Leu Ala Ala Ser Phe Val Gly																																																																					
35	40	45		Asn Ile Val Leu Ala Leu Val Leu Gln Arg Lys Pro Gln Leu Leu Gln		50	55	60		Val Thr Asn Arg Phe Ile Phe Asn Leu Leu Val Thr Asp Leu Leu Gln		65	70	75	80	Ile Ser Leu Val Ala Pro Trp Val Val Ala Thr Ser Val Pro Leu Phe		85	90	95		Trp Pro Leu Asn Ser His Phe Cys Thr Ala Leu Val Ser Leu Thr His		100	105	110		Leu Phe Ala Phe Ala Ser Val Asn Thr Ile Val Val Val Ser Val Asp		115	120	125		Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr		130	135	140		Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile		145	150	155	160	Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp		165	170	175		Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr		180	185	190													
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Asn Ile Val Leu Ala Leu Val Leu Gln Arg Lys Pro Gln Leu Leu Gln																																																																					
50	55	60		Val Thr Asn Arg Phe Ile Phe Asn Leu Leu Val Thr Asp Leu Leu Gln		65	70	75	80	Ile Ser Leu Val Ala Pro Trp Val Val Ala Thr Ser Val Pro Leu Phe		85	90	95		Trp Pro Leu Asn Ser His Phe Cys Thr Ala Leu Val Ser Leu Thr His		100	105	110		Leu Phe Ala Phe Ala Ser Val Asn Thr Ile Val Val Val Ser Val Asp		115	120	125		Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr		130	135	140		Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile		145	150	155	160	Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp		165	170	175		Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr		180	185	190																			
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Val Thr Asn Arg Phe Ile Phe Asn Leu Leu Val Thr Asp Leu Leu Gln																																																																					
65	70	75	80	Ile Ser Leu Val Ala Pro Trp Val Val Ala Thr Ser Val Pro Leu Phe		85	90	95		Trp Pro Leu Asn Ser His Phe Cys Thr Ala Leu Val Ser Leu Thr His		100	105	110		Leu Phe Ala Phe Ala Ser Val Asn Thr Ile Val Val Val Ser Val Asp		115	120	125		Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr		130	135	140		Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile		145	150	155	160	Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp		165	170	175		Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr		180	185	190																									
75	80																																																																				
Ile Ser Leu Val Ala Pro Trp Val Val Ala Thr Ser Val Pro Leu Phe																																																																					
85	90	95		Trp Pro Leu Asn Ser His Phe Cys Thr Ala Leu Val Ser Leu Thr His		100	105	110		Leu Phe Ala Phe Ala Ser Val Asn Thr Ile Val Val Val Ser Val Asp		115	120	125		Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr		130	135	140		Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile		145	150	155	160	Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp		165	170	175		Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr		180	185	190																															
95																																																																					
Trp Pro Leu Asn Ser His Phe Cys Thr Ala Leu Val Ser Leu Thr His																																																																					
100	105	110		Leu Phe Ala Phe Ala Ser Val Asn Thr Ile Val Val Val Ser Val Asp		115	120	125		Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr		130	135	140		Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile		145	150	155	160	Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp		165	170	175		Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr		180	185	190																																					
110																																																																					
Leu Phe Ala Phe Ala Ser Val Asn Thr Ile Val Val Val Ser Val Asp																																																																					
115	120	125		Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr		130	135	140		Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile		145	150	155	160	Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp		165	170	175		Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr		180	185	190																																											
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Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr																																																																					
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140																																																																					
Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile																																																																					
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Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp																																																																					
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Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr																																																																					
180	185	190																																																																			
190																																																																					

Thr Ile Leu Ser Val Val Ser Phe Ile Val Ile Pro Leu Ile Val Met
195 200 205

Ile Ala Cys Tyr Ser Val Val Phe Cys Ala Ala Arg Arg Gln His Ala
210 215 220

Leu Leu Tyr Asn Val Lys Arg His Ser Leu Glu Val Arg Val Lys Asp
225 230 235 240

Cys Val Glu Asn Glu Asp Glu Glu Gly Ala Glu Lys Lys Glu Glu Phe
245 250 255

Gln Asp Glu Ser Glu Phe Arg Arg Gln His Glu Gly Glu Val Lys Ala
260 265 270

Lys Glu Gly Arg Met Glu Ala Lys Asp Gly Ser Leu Lys Ala Lys Glu
275 280 285

Gly Ser Thr Gly Thr Ser Glu Ser Ser Val Glu Ala Arg Gly Ser Glu
290 295 300

Glu Val Arg Glu Ser Ser Thr Val Ala Ser Asp Gly Ser Met Glu Gly
305 310 315 320

Lys Glu Gly Ser Thr Lys Val Glu Glu Asn Ser Met Lys Ala Asp Lys
325 330 335

Gly Arg Thr Glu Val Asn Gln Cys Ser Ile Asp Leu Gly Glu Asp Asp
340 345 350

Met Glu Phe Gly Glu Asp Asp Ile Asn Phe Ser Glu Asp Asp Val Glu
355 360 365

Ala Val Asn Ile Pro Glu Ser Leu Pro Pro Ser Arg Arg Asn Ser Asn
370 375 380

Ser Asn Pro Pro Leu Pro Arg Cys Tyr Gln Cys Lys Ala Ala Lys Val
385 390 395 400

Ile Phe Ile Ile Ile Phe Ser Tyr Val Leu Ser Leu Gly Pro Tyr Cys
405 410 415

Phe Leu Ala Val Leu Ala Val Trp Val Asp Val Glu Thr Gln Val Pro
420 425 430

Gln Trp Val Ile Thr Ile Ile Trp Leu Phe Phe Leu Gln Cys Cys
435 440 445

Ile His Pro Tyr Val Tyr Gly Tyr Met His Lys Thr Ile Lys Lys Glu
450 455 460

Ile Gln Asp Met Leu Lys Lys Phe Phe Cys Lys Glu Lys Pro Pro Lys
465 470 475 480

Glu Asp Ser His Pro Asp Leu Pro Gly Thr Glu Gly Gly Thr Glu Gly
485 490 495

Lys Ile Val Pro Ser Tyr Asp Ser Ala Thr Phe Pro Ala Ile Ser Ala
500 505 510

Glu Phe His His Thr Gly Leu Val Asp Pro Ser Ser Val Pro Ser Leu
515 520 525

Gly Cys Arg Ser Met Gly Cys Leu Gly Asn Ser Lys Thr Glu Asp Gln
530 535 540

Arg Asn Glu Glu Lys Ala Gln Arg Glu Ala Asn Lys Lys Ile Glu Lys
545 550 555 560
Gln Leu Gln Lys Asp Lys Gln Val Tyr Arg Ala Thr His Arg Leu Leu
565 570 575
Leu Leu Gly Ala Gly Ser Gly Lys Ser Thr Ile Val Lys Gln Met
580 585 590
Arg Ile Leu His Val Asn Gly Phe Asn Gly Glu Gly Glu Glu Asp
595 600 605
Pro Gln Ala Ala Arg Ser Asn Ser Asp Gly Glu Lys Ala Thr Lys Val
610 615 620
Gln Asp Ile Lys Asn Asn Leu Lys Glu Ala Ile Glu Thr Ile Val Ala
625 630 635 640
Ala Met Ser Asn Leu Val Pro Pro Val Glu Leu Ala Asn Pro Glu Asn
645 650 655
Gln Phe Arg Val Asp Tyr Ile Leu Ser Val Met Asn Val Pro Asn Phe
660 665 670
Asp Phe Pro Pro Glu Phe Tyr Glu His Ala Lys Ala Leu Trp Glu Asp
675 680 685
Glu Gly Val Arg Ala Cys Tyr Glu Arg Ser Asn Glu Tyr Gln Leu Ile
690 695 700
Asp Cys Ala Gln Tyr Phe Leu Asp Lys Ile Asp Val Ile Lys Gln Ala
705 710 715 720
Asp Tyr Val Pro Ser Asp Gln Asp Leu Leu Arg Cys Arg Val Leu Thr
725 730 735
Ser Gly Ile Phe Glu Thr Lys Phe Gln Val Asp Lys Val Asn Phe His
740 745 750
Met Phe Asp Val Gly Gly Gln Arg Asp Glu Arg Arg Lys Trp Ile Gln
755 760 765
Cys Phe Asn Asp Val Thr Ala Ile Ile Phe Val Val Ala Ser Ser Ser
770 775 780
Tyr Asn Met Val Ile Arg Glu Asp Asn Gln Thr Asn Arg Leu Gln Glu
785 790 795 800
Ala Leu Asn Leu Phe Lys Ser Ile Trp Asn Asn Arg Trp Leu Arg Thr
805 810 815
Ile Ser Val Ile Leu Phe Leu Asn Lys Gln Asp Leu Leu Ala Glu Lys
820 825 830
Val Leu Ala Gly Lys Ser Lys Ile Glu Asp Tyr Phe Pro Glu Phe Ala
835 840 845
Arg Tyr Thr Thr Pro Glu Asp Ala Thr Pro Glu Pro Gly Glu Asp Pro
850 855 860
Arg Val Thr Arg Ala Lys Tyr Phe Ile Arg Asp Glu Phe Leu Arg Ile
865 870 875 880
Ser Thr Ala Ser Gly Asp Gly Arg His Tyr Cys Tyr Pro His Phe Thr

885

890

895

Cys Ala Val Asp Thr Glu Asn Ile Arg Arg Val Phe Asn Asp Cys Arg
900 905 910

Asp Ile Ile Gln Arg Met His Leu Arg Gln Tyr Glu Leu Leu
915 920 925

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Asp Cys Gly Leu Phe
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Cys Gly Thr Gly Cys Thr Gly Cys Cys Thr Gly Ala Gly Cys Gly Ala
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Gly Gly Ala Gly
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Gly Ala Thr Cys Gly Gly Ala Thr Cys Cys Thr Thr Ala Gly Ala Ala
1 5 10 15

Cys Ala Gly Gly Cys Cys Gly Cys Ala Gly Thr Cys Cys Thr Thr Cys
20 25 30

Ala Gly Gly Thr Thr Cys Ala Gly Cys Thr Gly Cys Ala Gly Gly Ala
35 40 45

Thr Gly Gly Thr Gly
50